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FINAL REPORT

EXTENSION OF OXYGEN TOLERANCE IN MAN

(PREDICTIVE STUDIES VI)

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TABLE OF CONTENTS

	Page
SUMMARY AND HIGHLIGHTS OF FINAL REPORT	1
OPTIMIZATION OF OXYGEN TOLERANCE EXTENSION IN ANIMALS	1
Rates of recovery from oxygen poisoning during intermittent exposure	1
Intermittent exposure patterns with the same oxygen:normoxic ratio	1
Relevance of animal data to oxygen tolerance extension in man	2
EXTENSION OF OXYGEN TOLERANCE IN MAN	2
Organ Specific Responses to Intermittent Exposure on a 60:15 Oxygen:Normoxic Pattern at 2.0 ATA	2
Effects on visual function	3
Effects on pulmonary symptoms and function	3
Organ Specific Responses to Intermittent Exposure on a 30:30 Oxygen:Normoxic Pattern at 2.0 ATA	4
Effects on visual function	5
Effects on pulmonary symptoms and function	5
Interpretation of Observed Results	6
Operational Relevance of Observed Results	8
INTRODUCTION TO BODY OF FINAL REPORT	9
Influence of pressure and duration of hyperoxic exposure	9
Practical use of oxygen at toxic high pressures	10
Defining human organ tolerance to continuous oxygen exposure	10
Oxygen tolerance extension by programmed interruption of oxygen exposure	11
Integration of animal and human investigation of oxygen tolerance extension	11

METHODS	12
OPTIMIZATION OF OXYGEN TOLERANCE EXTENSION IN ANIMALS	12
Exposure Conditions	12
Animals	12
Oxygen Tolerance Indices in the Rat	13
Survival time	13
Convulsion time	13
Organ specific indices of oxygen tolerance	13
EXTENSION OF OXYGEN TOLERANCE IN MAN	13
Intermittent Exposure on the 60:15 Oxygen:Normoxic Pattern	14
Intermittent Exposure on the 30:30 Oxygen:Normoxic Pattern	14
Subjects	15
Gas Administration System	15
Central Nervous System Function	16
Electroencephalography	16
Mental performance	16
Visual Function	16
Electroretinography	16
Perimetry	16
Visual evoked cortical responses	17
Visual acuity	17
Accommodation	17
Pupilometry	17
Ventilation and Gas Exchange	17
Arterial Blood Gases	18
Body Temperature	18
Pulmonary Function	18

Cardiovascular Function	18
Electrocardiogram	18
Cardiac output	18
Blood pressure	18
Orthostatic maneuver	19
Statistical Analysis	19
RESULTS AND DISCUSSION	20
ANIMAL STUDIES	20
Effects of Intermittent Oxygen Exposure on Survival Time at 4.0, 2.0, and 1.5 ATA	20
Intermittent patterns with 20-min oxygen exposure periods	20
Intermittent patterns with 60-min oxygen exposure periods	20
Intermittent patterns with 120-min oxygen exposure periods	20
Intermittent patterns with 1:1 oxygen:normoxic ratios	21
Intermittent patterns with 2:1 oxygen:normoxic ratios	21
Intermittent patterns with 4:1 oxygen:normoxic ratios	22
Summary and Interpretations of Animal Data	22
Relationships of survival time increments to normoxic interval durations	22
Rates of recovery in relation to exposure patterns	23
HUMAN STUDIES	24
EVALUATION OF ORGAN SPECIFIC RESPONSES TO INTERMITTENT EXPOSURE ON A 60:15 OXYGEN:NORMOXIC PATTERN AT 2.0 ATA	24
Exposure Duration and Symptoms	24
Effects on Brain Electrical Activity	24
Effects on Auditory-Vestibular Function	24
Mental Performance and Psychomotor Function	25

Effects on Visual Function	25
Rate and Pattern of Pulmonary Ventilation	27
Effects on Pulmonary Function	28
Rate of decrease in vital capacity	28
Post-exposure evaluation of pulmonary function	29
Lung expiratory function and compliance	29
Lung diffusing capacity and arterial oxygenation	30
Effects on Respiratory and Skeletal Muscle Strength	31
Effects on Cardiovascular Function and Body Temperature	31
EVALUATION OF ORGAN SPECIFIC RESPONSES TO INTERMITTENT EXPOSURE ON A 30:30 OXYGEN:NORMOXIC PATTERN AT 2.0 ATA	32
Exposure Duration and Symptoms	32
Effects on Brain Electrical Activity	32
Effects on Auditory-Vestibular Function	32
Mental Performance and Psychomotor Function	33
Effects on Visual Function	33
Rate and Pattern of Pulmonary Ventilation	34
Effects on Pulmonary Function	35
Rate of decrease in vital capacity	35
Post-exposure evaluation of pulmonary function	36
Effects on Respiratory and Skeletal Muscle Strength	36
Effects on Cardiovascular Function and Body Temperature	37
INTERPRETATION AND RELEVANCE OF RESULTS	38
Comparative Rates of Development of Visual and Pulmonary Effects of Oxygen Toxicity during Continuous and Intermittent Oxygen Exposure at 2.0 ATA	38
Extension of Oxygen Tolerance on the 60:15 Oxygen:Normoxic Sequence	39
Extension of Oxygen Tolerance on the 30:30 Oxygen:Normoxic Sequence	40

Possible Mechanisms for Oxygen Tolerance Extension during Intermittent Exposure	41
Operational Relevance of Observed Results	43



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SUMMARY AND HIGHLIGHTS OF FINAL REPORT

The Predictive Studies VI Program consisted of two related areas of research activity, integrated in design and performance, that were each based on an ongoing analysis of human organ oxygen tolerance data obtained from the continuous oxygen exposures of the prior Predictive Studies V Program. The two research areas effectively blended broad investigation of systematically varied intermittent exposure patterns in animals with very selective evaluation of specific exposure patterns in man.

OPTIMIZATION OF OXYGEN TOLERANCE EXTENSION IN ANIMALS

In order to determine rates of recovery from different degrees of oxygen poisoning, oxygen exposure periods of 20, 60, or 120 min were systematically alternated with a constant normoxic interval whose duration was also varied systematically in different exposures. Durations of normoxic intervals were selected to provide the same hyperoxic:normoxic ratios for each of the three oxygen exposure periods. This was done to determine whether the toxic events accumulated over a relatively long oxygen exposure (120 min) reversed on return to normoxia at the same rate as those that accumulated during shorter oxygen exposures (60 or 20 min).

Intact animal responses to the selected patterns of intermittent exposure were determined at oxygen pressures of 1.5, 2.0, and 4.0 ATA. This range of oxygen pressures allowed comparison of results obtained at 1.5 and 2.0 ATA, where effects of pulmonary oxygen toxicity were not influenced by concurrent convulsions, with comparable data obtained at 4.0 ATA, where there were prominent interactions between pulmonary and central nervous system effects of oxygen toxicity.

Rates of recovery from oxygen poisoning during intermittent exposure. Overall analysis of the data obtained at all three oxygen pressures revealed a high degree of internal consistency. With only a few exceptions, median survival time increased linearly at each pressure as the duration of the normoxic recovery interval was lengthened while holding the oxygen exposure period constant. Comparison of the slopes of the curves for each oxygen exposure period at each pressure revealed that recovery occurred most rapidly after the 20-min oxygen periods and least rapidly after the 120-min periods. It also indicated that rate of recovery for a given oxygen exposure period occurred more rapidly at a lower oxygen pressure. Although these relationships were anticipated qualitatively, the consistency of the data provided an unequivocal, quantitative description of the rate of recovery under each set of experimental conditions.

Intermittent exposure patterns with the same oxygen:normoxic ratio. Analysis of survival time responses to different

intermittent exposure patterns whose oxygen and normoxic periods have the same ratio (e.g. 20:5 and 60:15 both have a 4:1 ratio) showed that, within limits, similar results were obtained at the same oxygen pressure. During intermittent exposures at oxygen pressures of 4.0 and 2.0 ATA, this generalization did not apply to patterns with 120-min oxygen periods (presumably due to the occurrence of toxic events that were not readily reversed during the subsequent normoxic recovery interval) or with 5-min normoxic intervals (presumably too short a time for adequate recovery). Operational application of the principle that similar extensions of oxygen tolerance can be obtained with intermittent exposure patterns whose oxygen and normoxic periods have the same ratio will provide an empirical basis for selection of equally effective intermittent exposure patterns, within appropriate limits, to provide the shortest possible normoxic interval or the longest possible oxygen exposure period.

Relevance of animal data to oxygen tolerance extension in man. Quantitative relationships defined in rats by empirical curves that describe survival time extension by intermittent oxygen exposure will not be directly applicable to man. However, it is considered that the analytical methods used to derive the descriptive curves from data obtained in rats will also be useful for the analysis of human data obtained in early, reversible stages of oxygen poisoning over an appropriate range of oxygen pressures and intermittent exposure patterns. Although the number of human intermittent oxygen exposures will necessarily be much more selective and limited than was possible in rats, the volume of pathophysiological information obtained from each exposure will be immensely greater. The inherently limited survival time data will be replaced by quantitative measurements of oxygen effects on multiple organ systems and functions. The rat data should also provide guidelines relevant to the determination of optimum durations for the alternating oxygen periods and normoxic intervals that, with appropriate adjustment, should aid in the development of optimum patterns of intermittent oxygen exposure for extension of organ-specific oxygen tolerance in man.

EXTENSION OF OXYGEN TOLERANCE IN MAN

Organ Specific Responses to Intermittent Exposure on a 60:15 Oxygen:Normoxic Pattern at 2.0 ATA

Of the eight subjects who were exposed intermittently to oxygen at 2.0 ATA on the 60:15 oxygen:normoxic pattern, primary emphasis was placed on statistical analysis and interpretation of average data for the six individuals who were exposed for 11.4 to 15.0 oxygen hours (mean 13.6 hours) and developed objective visual and pulmonary manifestations of oxygen toxicity. In agreement with the results of the previous continuous oxygen exposures of Predictive Studies V, the eye and the lung were the

primary targets of oxygen toxicity during intermittent oxygen exposure at 2.0 ATA.

Effects on visual function. With few exceptions, the effects of intermittent oxygen exposure at 2.0 ATA on visual function were qualitatively similar to the effects observed previously in the continuous oxygen exposures of Predictive Studies V. Visual acuity, nearpoint accommodation, and pupil diameter were not detectably affected by intermittent oxygen exposure at 2.0 ATA. In contrast to the previous observation of no change during and after continuous oxygen exposure at 2.0 ATA, however, latency of the visual evoked cortical response was significantly increased at the end of intermittent oxygen exposure by an average value of 5.79 milliseconds (5.1%). It is possible that this small, isolated change in visual evoked cortical response was induced by fatigue rather than any specific effect of oxygen toxicity.

During intermittent exposure to oxygen at 2.0 ATA, as in the previous continuous exposures, peripheral visual field area and the electroretinographic b-wave amplitude were the components of visual function that were affected most consistently by oxygen toxicity. In the six subjects who had the longest oxygen exposures, average visual field area was significantly reduced by 13.9% at an exposure duration of 11.2 oxygen hours. It then recovered partially to be reduced by 8.4% during the last hour of exposure. An equal decrement during the early post-exposure period was not statistically significant.

Electroretinographic responses (b-wave amplitude) to three different light intensities, with only two exceptions, were significantly reduced during the last hour of oxygen exposure and were further reduced during the early post-exposure period. Using an overall average of responses to all three light intensities at each time of measurement, b-wave amplitude fell progressively during intermittent oxygen exposure to a decrement of 31.9% at 13.6 oxygen hours in six subjects, compared with the previous observation of an average decrement of 39.4% in seven subjects at 9.4 hours of continuous exposure in Predictive Studies V.

Effects on pulmonary symptoms and function. An opportunity to test in man the hypothesis that equivalent extensions of oxygen tolerance are provided by intermittent hyperoxia patterns whose oxygen:normoxic periods have the same ratio was provided by the availability of the previous study of Hendricks et al (1) in which the extension of pulmonary tolerance to oxygen exposure at 2.0 ATA on a 20:5 intermittent exposure pattern was measured in normal men. Pulmonary responses to the 60:15 pattern of intermittent exposure in the present Predictive Studies VI Program were compared with the previously observed responses to the 20:5 pattern, and average responses from both series of

intermittent exposures were compared with results of the continuous oxygen exposures of Predictive Studies V.

Rate of development of pulmonary oxygen poisoning during either continuous or intermittent oxygen exposure at 2.0 ATA was monitored subjectively at regular intervals by repeated surveys of pulmonary symptoms. Each symptom survey included individual ratings of cough, chest pain, chest tightness, and shortness of breath as absent (0), mild (1+), moderate (2+), or severe (3+). Overall average ratings that included all four symptoms and all subjects in each group were calculated and plotted against exposure duration for continuous and both intermittent exposures. Results showed that both the 20:5 and 60:15 patterns of intermittent oxygen exposure delayed the development of pulmonary symptoms by degrees that were remarkably similar given the subjective nature of the available information.

As an objective measure of toxic effects on pulmonary function, average decrements in vital capacity were plotted against exposure duration for continuous and intermittent exposure. With respect to the curve for continuous exposure (N=16), both average curves for intermittent exposure reflected increments in pulmonary oxygen tolerance, but the 20:5 exposure pattern (N=5) appeared to be slightly more effective than the 60:15 pattern (N=6). Comparison of individual responses to the 60:15 intermittent exposure pattern with the average curves for continuous exposure and the 20:5 intermittent exposure showed that rates of decrease in vital capacity for four subjects on the 60:15 pattern were similar to the average curve for the 20:5 intermittent exposure pattern, while rates of vital capacity decrement for the other two subjects were closer to the average curve for continuous oxygen exposure. These results are consistent with the interpretation that equivalent extensions of pulmonary oxygen tolerance are provided by both the 60:15 and the 20:5 intermittent exposure patterns for most individuals, but that an oxygen exposure period of 60 minutes is too long for a minority of presumably more sensitive individuals.

Organ Specific Responses to Intermittent Exposure on a 30:30 Oxygen:Normoxic Pattern at 2.0 ATA

It was anticipated that the 30:30 intermittent exposure pattern would extend oxygen tolerance significantly beyond that provided by the 60:15 pattern, because it concurrently reduced the toxic period by half and doubled the time allowed for recovery in each successive cycle. An exposure duration of 15.0 oxygen hours, requiring a total of 29.5 continuous hours at 2.0 ATA, was selected as the maximum duration that was logistically feasible. Of the six intermittent exposures that were completed on the 30:30 pattern, four were continued for the planned duration of 15.0 oxygen hours, and the other 2 were stopped at 13.0 hours. Although symptoms remained generally mild in most

subjects, the first exposure was stopped at 13.0 oxygen hours when the subject appeared to be developing prominent decrements in visual and pulmonary function. The last exposure was also stopped at 13.0 oxygen hours when the subject became extremely anxious in association with chest tightness and shortness of breath. Reversible decrements in visual and pulmonary function were again the primary objective manifestations of oxygen poisoning.

Effects on visual function. Average values for visual evoked cortical responses, nearpoint accommodation, and pupil diameter were similar before, during, and after intermittent oxygen exposure. Except for a minor change from 20/25 to 20/30 in one subject, visual acuities were identical before, during, and after exposure.

Changes in peripheral visual field area on the 30:30 intermittent exposure sequence were less consistent than previously observed during either continuous exposure or intermittent exposure on the 60:15 sequence. With respect to the control measurement at the start of oxygen exposure, average values were reduced by 5.5% at 8.0 oxygen hours, increased by 2.5% at 10.0 hours, reduced again by 6.4% at 13.0 hours, and decreased by 5.3% at the end of oxygen exposure. With respect to the pre-exposure control value, average visual field area was increased by 3.1% during the early post-exposure period. None of the observed changes in visual field area were statistically significant.

Average changes in the electroretinographic b-wave amplitude on the 30:30 sequence also differed qualitatively and quantitatively from those found previously during either continuous or intermittent exposure. With respect to the initial control value, overall average responses to all three light intensities for the six subjects on the 30:30 sequence were essentially unchanged through 6.0 oxygen hours, fell abruptly to an average decrement of 19.5% at 8.0 hours, and then recovered progressively to reach an average decrement of only 3.3% at the end of the intermittent exposure. None of these changes were statistically significant. However, average responses to the intermediate light intensity, which were qualitatively similar to the overall average responses to all three intensities, were significantly reduced by 26.8% at 8.0 oxygen hours. Progressive recovery of b-wave amplitude during the second half of the intermittent exposure on the 30:30 sequence contrasted sharply with the concurrent progressive decrements observed during both continuous oxygen exposure and intermittent exposure on the 60:15 sequence.

Effects on pulmonary symptoms and function. As expected, pulmonary symptoms developed more slowly and were less severe on the 30:30 sequence than for the previous intermittent exposures

on the 60:15 sequence. Average symptom ratings at the end of each of the three exposure series were 1.0 at 14.3 oxygen hours on the 30:30 sequence, 2.0 at 13.6 oxygen hours on the 60:15 sequence, and 2.1 at 9.2 hours of continuous exposure.

Average vital capacity decrements for the six subjects exposed intermittently on the 30:30 sequence initially were nearly superimposed on the curve for continuous exposure to reach an average decrement of 6.0% at 8.0 oxygen hours, then remained essentially constant, crossing the curve for intermittent exposure on the 60:15 sequence at 11.1 hours to end at an average decrement of 6.1% at 14.3 oxygen hours. Individual changes in vital capacity at the end of oxygen exposure varied from -9.2% to +1.4% of the initial control value. All of the changes in vital capacity observed from 8.0 to 14.3 oxygen hours were statistically significant. Although intermittent exposure on the 30:30 sequence allowed nearly 15 hours of oxygen breathing at 2.0 ATA with a relatively small change in vital capacity, as predicted, the observation of vital capacity decrements that initially exceeded those found previously for the 60:15 sequence was not expected.

Interpretation of Observed Results

In agreement with results of the previous continuous oxygen exposures at 2.0 ATA in Predictive Studies V, intermittent oxygen exposure at 2.0 ATA on either the 60:15 or 30:30 oxygen:normoxic sequence had little or no effect on brain electrical activity, auditory and vestibular function, mental performance, and psychomotor function. The most prominent toxic effects of intermittent oxygen exposure at 2.0 ATA, again in agreement with the effects of continuous exposure, were manifested as significant alterations in specific aspects of visual function (retinal electrical activity and peripheral vision) and in several indices of pulmonary function.

With respect to the 60:15 oxygen:normoxic sequence, the 30:30 sequence halved the toxic oxygen period and doubled the normoxic recovery interval. On the basis of general principles of oxygen tolerance extension by intermittent exposure, and in agreement with results of the 60:15 exposure sequence and the extensive animal studies that were completed previously under this Program, it was anticipated that visual and pulmonary effects of oxygen toxicity would be undetectable or small in magnitude throughout the 15.0 oxygen exposure hours that were planned for the 30:30 sequence (total exposure duration of 29.5 hours). It was therefore surprising when both ERG b-wave amplitude and vital capacity decreased initially at faster rates than those found during the previously completed 60:15 exposure sequence.

Although the biochemical mechanisms responsible for extension of oxygen tolerance by systematic alternation of oxygen and normoxic exposure periods are not known, it is likely that partial reversals of toxic effects during the normoxic recovery periods play a major role. The observation that initial decrements in ERG b-wave amplitude and vital capacity were stabilized or partially reversed during continued intermittent oxygen exposure on the 30:30 sequence indicates that during the final hours of exposure the degree of recovery that occurred during each normoxic interval must have equalled or exceeded the cumulative toxic effects caused by the preceding oxygen period for both visual and pulmonary manifestations of oxygen toxicity. These apparently enhanced capacities for recovery from oxygen poisoning were not evident during the first 8 to 10 hours of exposure, when the degrees of visual and pulmonary oxygen tolerance extension provided by the 60:15 exposure sequence were overtly equal to or exceeded those provided by the 30:30 sequence.

Our results appear to indicate that the 60:15 sequence afforded greater protection of oxygen tolerance than the 30:30 sequence during the initial hours of intermittent exposure, but eventually became overwhelmed as the exposure continued. On the other hand, the 30:30 sequence was relatively ineffective initially, but then became sufficiently effective to stabilize or reverse earlier decrements in both visual and pulmonary function during the final hours of intermittent exposure. It is now well established that exposure to hyperoxia increases the rates of production of active species that are concurrently opposed by a variety of antioxidant defenses. At a sufficiently high oxygen pressure and/or for a sufficiently prolonged duration of exposure, oxidant damage to cells and tissues occurs when antioxidant defenses are overwhelmed. Periodic interruption of oxygen exposure by restoration of normoxia should allow antioxidant defenses to be maintained or possibly even enhanced.

One possible interpretation of our results can be based on the hypothesis that extension of oxygen tolerance by intermittent exposure depends not only upon cyclical periods of recovery from oxygen poisoning, but also involves the concurrent augmentation of antioxidant defenses or some other means of oxygen tolerance enhancement. Previous animal studies have shown that antioxidant defenses can be enhanced by sufficiently prolonged exposure to toxic, sublethal levels of hyperoxia. It is possible that the 60:15 intermittent exposure pattern, by virtue of an inherently greater level of toxicity, initiated the enhancement of antioxidant defenses at an earlier time than the 30:30 pattern, but was unable to sustain the level of production required for continued protection. If the proposed hypothesis can be confirmed, it may be possible to increase the benefits of intermittent exposure by selecting appropriate patterns for different parts of a prolonged exposure, or by basing the choice

of a single pattern on the expected duration of intermittent exposure.

Operational Relevance of Observed Results

Optimization of oxygen tolerance extension by intermittent hyperoxic exposure will provide prominent and permanent enhancement of Navy mission in diving operations, decompression methods, and hyperoxygenation therapy. The research results are relevant to both procedure and probability of success in all forms of Navy diving. Extension of CNS (visual) and pulmonary oxygen tolerance to increased oxygen pressures relates specifically and critically to both safety and operational effectiveness in undersea operations, as well as to improvement in therapy of gas lesion diseases. Although extension of oxygen tolerance by intermittent exposure has been studied only at rest to date, concurrent studies indicate that the adverse effects of exercise on oxygen tolerance may be avoided by preventing the hypercapnia and associated increments in brain blood flow and oxygen dose that occur during oxygen breathing at increased ambient pressures. Validation of this working hypothesis will provide a basis for extension of oxygen tolerance during exercise as well as at rest.

Our results show that both visual and pulmonary oxygen tolerance can be extended significantly at 2.0 ATA by systematic alternation of oxygen and normoxic exposure periods. They also show clearly for the first time in man or in animals that early toxic effects on the eye and lung can be stabilized or reversed at least partially during continued intermittent exposure with an appropriate combination of oxygen exposure and normoxic recovery periods. The extents to which such reversals will occur at other oxygen pressures and with other effects of oxygen toxicity remain to be determined. Elucidation of the mechanisms for such responses should provide information that can be widely exploited in the development of more effective means for extension of oxygen tolerance than those that are now available.

INTRODUCTION TO BODY OF FINAL REPORT

The toxicity of oxygen is the primary factor limiting effectiveness and safety in essentially all forms of diving. Oxygen is the vital force in metabolism, but at the same time it exerts toxic effects upon many of the critical life processes it sustains. Even in natural atmospheres, the continuous generation of oxygen free radicals produces destructive effects upon enzymes, metabolic and membrane functions, and other biological processes. Intrinsic antioxidant mechanisms normally scavenge these free radicals, preventing gross cumulative damage. However, as high oxygen pressures are used in diving, in decompression, in treatment of decompression sicknesses, and in hyperbaric therapy generally, the intrinsic antioxidant defense mechanisms are overwhelmed, and evident oxygen poisoning can develop. This can occur whether the high respired oxygen pressure is provided as pure oxygen, as air, or in mixtures of oxygen with helium or nitrogen as the inert carrier (or diluent) gas. These toxic actions of hyperoxia must, at sufficient pressure and duration of continuous exposure, be considered capable of disrupting or destroying the vital processes of any human cell.

Although oxygen must be considered to have universally toxic properties with effects upon multiple chemical reactions, cells, tissues, and organs, the best recognized limiting expressions of oxygen poisoning in man are pulmonary symptoms and functional degradations, and the central nervous system electrical disruptions which produce generalized convulsions and unconsciousness (2,3). These overt and readily recognizable effects are not to be considered indicative of higher "sensitivity" of brain cortex and lung to oxygen poisoning. They simply represent grossly obvious effects with particular hazard in underwater operations (4). In the prior Predictive Studies V Program, an intensive investigation for other important but less evident limiting forms of oxygen poisoning was carried out, and preliminary results have been reported (5-8).

Influence of pressure and duration of hyperoxic exposure.
The toxic chemical effects of high oxygen pressures, simultaneously exerted upon and inactivating multiple intracellular and membrane enzyme systems, increase progressively in degree (severity) as duration of oxygen exposure lengthens. The rates of enzyme inactivation, with consequent failure of cell and organ function, are speeded progressively as the oxygen partial pressure of an exposure is increased. If all cells and enzymes were both (a) equally sensitive to oxygen toxicity, and (b) exposed at their locations in the body to the same partial pressures of oxygen, prediction of tolerance to continuous oxygen exposure would be relatively simple. However, each enzyme system has its own sensitivity to oxygen poisoning. In addition, the same enzyme system in different cell forms (brain, retina, lung,

kidney) has a different intracellular chemical environment and even a different level of exposure to oxygen (3). Finally, the enzymatic composition of cells in different vital organs is not uniform. For all these reasons, the detectable consequences of cellular oxygen poisoning are grossly different, function-by-function (lung, brain, eye, muscle, ear, heart). Rates of onset and recovery must also be considered grossly different, function-by-function (3).

Practical use of oxygen at toxic high pressures. In spite of its toxicity, oxygen at high pressures can be safely and effectively used in diving and therapy. As with many drugs, an adverse effect of oxygen does not become disturbing immediately, and mild effects disappear when oxygen use is discontinued. The safe periods for practical use of oxygen breathing are not technically to be considered "Latent Periods", in spite of long use of this term. Rather these are periods in which the degree of toxic action is so small that it produces no symptoms or other significant effects. Since mild effects develop slowly and disappear when oxygen use is discontinued, repeated daily (or more frequently) exposure to moderate hyperoxia is practical in diving as well as in therapy. Rather, initial exposures can be considered to represent a useful period of slowly progressing, asymptomatic changes from which recovery can be prompt and complete. The practical use of high oxygen pressures in diving is based upon the inconsequential influences of oxygen during initial periods of exposure. Extending this initial period of tolerable or inconsequential toxicity will provide large extensions of diving capability.

Defining human organ tolerance to continuous oxygen exposure. The previous Navy-supported, collaborative Predictive Studies V Program was performed to determine the rates of development and recovery in oxygen poisoning produced by uninterrupted oxygen breathing over essentially the full range of oxygen exposure useful in diving and hyperbaric therapy. This multiyear, multidisciplinary Program investigated measurable physiologic and toxic effects of oxygen upon selected organ and tissue functions at 0.2, 1.5, 2.0, 2.5, and 3.0 ATA of inspired oxygen. This Program represented the first systematic investigation of human pulmonary oxygen poisoning at oxygen pressures greater than 2.0 ATA (5-8). It represented the only definitive investigation at pressures greater than 1.0 ATA of oxygen poisoning effects in other human organ systems and tissues, including brain, heart, liver, kidney, skeletal muscle, and endocrine organs.

This extensive investigation of specific organ oxygen tolerance, which followed over a decade of prior investigations in animals and tissues to assure adequacy of scope and safety in human experiment, has provided essential guidance for continuous hyperoxic exposures in various diving and therapy situations.

The results obtained will be of permanent usefulness in defining the maximum capability for continuous oxygen exposure. This investigation additionally serves as the required baseline for the present Predictive Studies VI Program emphasis on optimal extensions of human organ oxygen tolerance through use of programmed interruptions of oxygen exposure over a useful range of high inspired oxygen pressures.

Oxygen tolerance extension by programmed interruption of oxygen exposure. A key concept emphasized early in this Institute's continuing Oxygen Research Program is that, following a toxic exposure to hyperoxia, a sufficient interval of normoxia will allow for recovery and permit useful hyperoxic exposure again (9,10). The duration of the recovery interval required will depend upon the rate of onset, nature, and degree of induced poisoning (and hence upon the rate of recovery). By systematic investigation of rates of poisoning of different functions or systems, at different oxygen exposure pressures, with tracking as practical of the rates of recovery, it should be possible to define (a) tolerance of critical functions to oxygen; and (b) optimal programs of intermittent oxygen exposure, allowing maximum effective use of oxygen at various pressures important to therapy and undersea operations.

Integration of animal and human investigation of oxygen tolerance extension. Although oxygen tolerance data obtained in the rat cannot be applied quantitatively to man, it can provide valuable guidelines for the selection of intermittent exposure patterns to be evaluated in man. Attempts to determine optimum intermittent exposure patterns solely in man would not only be prohibitively expensive, but it would also involve unacceptable risk of the occurrence of unexpected forms or degrees of oxygen poisoning. The ultimate objective of oxygen tolerance extension in man can be reached most effectively and safely by parallel design and concurrent performance of both animal and human investigation, thereby maximizing the opportunity for integration of findings.

METHODS

The Predictive Studies VI Program consisted of two related areas of research activity, integrated in design and performance, that were each based on an ongoing analysis of human organ oxygen tolerance data obtained from the continuous oxygen exposures of the prior Predictive Studies V Program. The two research areas effectively blended broad investigation of systematically varied intermittent exposure patterns in animals with very selective evaluation of specific exposure patterns in man.

OPTIMIZATION OF OXYGEN TOLERANCE EXTENSION IN ANIMALS

In order to determine rates of recovery from different degrees of oxygen poisoning, oxygen exposure periods of 20, 60, or 120 min were systematically alternated with a constant normoxic interval whose duration was also varied systematically in different exposures. Durations of normoxic intervals were selected to provide the same hyperoxic:normoxic ratios for each of the three oxygen exposure periods. This was done to determine whether the toxic events accumulated over a relatively long oxygen exposure (120 min) reversed on return to normoxia at the same rate as those that accumulated during shorter oxygen exposures (60 or 20 min).

Durations of the oxygen periods and normoxic intervals for intermittent exposure patterns that have been studied at 1.5, 2.0, and 4.0 ATA are shown in Appendix Table 1. The selected range of oxygen pressures allows comparison of results obtained at 1.5 and 2.0 ATA, where effects of pulmonary oxygen toxicity are not influenced by concurrent convulsions, with comparable data obtained at 4.0 ATA, where there are prominent interactions between pulmonary and central nervous system effects of oxygen toxicity.

Exposure Conditions

For each intermittent pattern, a group of 20 rats, housed individually in wire and plexiglass cages, was exposed in a steel hyperbaric chamber with large viewports. Chamber concentrations of oxygen and carbon dioxide were monitored continuously. During oxygen periods, oxygen concentration was maintained at 99-100%. Carbon dioxide concentrations were negligible during both oxygen and normoxic periods. Ambient temperature was maintained within a range of 22-25 °C. High gas flow rates were used at the start of each oxygen or normoxic period to provide a 98% change of inspired gas within 90 sec.

Animals

Male, specific pathogen-free, Charles River CD rats maintained on Ziegler rat and mouse diet were used in these

exposures. Average weights of the different exposure groups ranged from about 300 to 400 grams with an overall average of about 350 grams.

Oxygen Tolerance Indices in the Rat

Survival time. Elapsed oxygen time prior to cessation of breathing was determined by 24-hour monitoring of all 20 rats in each intermittent oxygen exposure. Although it is recognized that many interacting factors determine the lethal duration of exposure to any toxic oxygen pressure, survival time in a sufficiently large animal population is an important general index of oxygen tolerance, as it is for other toxic substances. At oxygen pressures of 1.5 and 2.0 ATA, pulmonary oxygen poisoning occurs in the absence of convulsions, while at 4.0 ATA there are prominent interactions between pulmonary effects of oxygen toxicity and the violent sympathetic activity associated with convulsions.

Convulsion time. The elapsed oxygen time before initial onset of seizures is also affected by many variables other than inspired oxygen pressure. During continuous or intermittent oxygen exposures at 4.0 ATA, however, onset of convulsions is a definite and usually an early manifestation of central nervous system oxygen poisoning.

Organ specific indices of oxygen tolerance. It is highly desirable to supplement data obtained from intact animals and man with information describing the state of several confirmed or potential organ-specific indices of oxygen tolerance in different degrees of oxygen poisoning. However, broad investigation of biochemical and histopathologic alterations in several critical organs during both continuous and intermittent oxygen exposures will be extremely costly and will require several years to complete. The high cost is determined primarily by the requirement for extensive measurement in multiple tissues, at multiple points of exposure and recovery, and in multiple patterns of exposure. The required investigations are therefore beyond the scope of this Predictive Studies VI Program.

EXTENSION OF OXYGEN TOLERANCE IN MAN

Organ specific responses to two different patterns of intermittent oxygen exposure at 2.0 ATA were evaluated in man. One pattern, which alternated 60-min oxygen exposure periods with 15-min normoxic recovery intervals, was evaluated to test the hypothesis that equivalent extensions of oxygen tolerance are provided by intermittent hyperoxia patterns whose oxygen:normoxic periods have the same ratio. A special opportunity to evaluate the ratio principle in man was provided by the availability of the previous study by Hendricks et al (1) in which the extension of pulmonary tolerance to oxygen exposure at 2.0 ATA on a 20:5

intermittent exposure pattern was measured in normal men. The second pattern of intermittent exposure, which alternated 30-min oxygen periods with 30-min normoxic intervals, was selected to complement the information obtained from the 60:15 pattern by testing the hypothesis that prominent improvement of oxygen tolerance extension in man could be obtained by reducing the toxic period by half and concurrently doubling the recovery interval.

Intermittent Exposure on the 60:15 Oxygen:Normoxic Pattern

Each experiment required 2 days for the intermittent oxygen exposure, preceded by a day of preparation, and followed by at least 3 days of post-exposure measurements. The experiment protocol for the 2 days of exposure is summarized in Appendix Figure 1. Much of the first day was required for subject preparation and pre-exposure control measurements. The intermittent oxygen exposure typically began about 1600 hours and continued overnight to end before noon the next day.

The sequence of measurements performed during the first and last hours of oxygen exposure is shown in Appendix Figure 2. Each measurement of a subset that was performed repeatedly during the intermittent oxygen exposure to monitor the onset and progression of toxic effects is denoted by an asterisk. The pre and post-exposure measurements included a comprehensive evaluation of pulmonary function in addition to the parameters measured during exposure.

Intermittent Exposure on the 30:30 Oxygen:Normoxic Pattern

The experiment protocol for the 30:30 oxygen:normoxic exposure pattern at 2.0 ATA is summarized in Appendix Figure 3. After a 5 to 6-hour period of subject preparation and control measurements, the intermittent oxygen exposure at 2.0 ATA was started at about 1200 hours and continued overnight to end at about 1800 hours on the next day. An additional 5-6 hours of pre-exposure control measurements obtained on 2 previous days are not shown on the graph. An exposure duration of 15 oxygen hours, requiring a total of 30 continuous hours at 2.0 ATA, was selected as the maximum duration that was logistically feasible.

Completion of the intermittent oxygen exposure at 2.0 ATA was followed at 1.0 ATA by a 7 to 8-hour period of post-exposure measurements that extended into the early morning hours of the next day. After a few hours of sleep, the subject was awakened at about 0800 hours for an additional 6-8 hours of post-exposure measurements, followed by shorter measurement periods on subsequent days. The total period of study for each subject on this protocol required 5 consecutive days for pre-exposure, exposure, and post-exposure measurements, with additional days

for medical evaluation of the subject, training, and follow-up measurements.

The sequence of measurements that were performed at the start and end of the intermittent oxygen exposure is shown in Appendix Figure 4. Each measurement denoted by an asterisk was part of a subset that was repeated at designated intervals during exposure to monitor the onset and progression of toxic effects. The 30-min duration of the oxygen period made it necessary to perform some of the measurements during the subsequent normoxic interval. The pre and post-exposure evaluation included ventilatory control measurements and a comprehensive evaluation of pulmonary function in addition to the measurements shown in Appendix Figure 4.

Subjects

Each subject received a comprehensive medical evaluation which included a medical history and physical examination, neuro-ophthalmologic evaluation, electrocardiogram, electroencephalogram, electroretinogram, visual acuity and fields, chest x-ray, urinalysis, and hematology profile. Informed consent was obtained on 2 separate occasions prior to oxygen-exercise exposure at 2.0 ATA. All procedures and measurements were approved by the Human Studies Committee of the University of Pennsylvania.

Gas Administration System

Oxygen from an external liquid source was piped into the chamber, humidified, and conducted to a 30-liter reservoir bag from which it was inspired by the subject through 1.0-inch i.d. corrugated plastic tubing. Normoxic gas (10.5% O₂ in N₂) was piped from an external premixed cylinder to a second humidifier and reservoir bag system inside the chamber. Transitions between oxygen and normoxic gas were accomplished by connecting the inside gas administration system to the appropriate reservoir bag and squeezing the bag to flush all connecting tubing up to the subject. Relative humidity of the inspired gas, measured at flow rates of about 10 to 50 L/min with a Cole-Palmer Model 3309-60 Thermo-hygrometer, was about 80% at chamber temperature.

Throughout most of the exposure, oxygen or normoxic gas was administered via a lightweight, plastic, non-rebreathing, oronasal facemask with an inflatable seal (Vital Signs Inc.). During the brief periods required to perform related visual measurements, the subject wore a noseclip and breathed oxygen via a mouthpiece, non-rebreathing assembly. Expired gas was conducted by corrugated plastic tubing to an overboard dump system, except when it was collected to measure gas exchange.

Mask oxygen concentration was monitored continuously with an Applied Electrochemistry Model SA-3 Electrochemical O₂ Meter. Mask FO₂ remained consistently above 0.98 except for occasional periods of about 10 seconds when the mask seal was transiently breached by subject movement. End-tidal carbon dioxide concentration was monitored with a Datex Model CD-101 CO₂ Analyzer.

Central Nervous System Function

Electroencephalography. Twelve channels of EEG were continuously recorded from 12 scalp electrodes onto a Grass Model 8-16 EEG machine and onto a magnetic tape recorder. A modified INT 10-20 system was used for electrode placement.

Mental performance. Mental and psychomotor function were evaluated at 1.0 ATA before and after each intermittent oxygen exposure, and at the start and end of intermittent exposure at 2.0 ATA. Specific tests that were used included a visual digit span test of short term memory ability, a key insertion test of finger dexterity ability, an operations test of number facility and general reasoning abilities, and a visual reaction time test of response speed ability. This sequence of four consecutive tests was administered and scored by computer over a 7-min period as a component of the Institute-developed Performance Measurement System (11).

Visual Function

Electroretinography. The electroretinogram (ERG) was obtained from the dark adapted (right) eye, using a Burian-Allen electrode that rested on a soft contact lens to prevent corneal abrasion. The retinal response was elicited by a 10-microsecond flash stimulus from a Grass Model PS22 Photostimulator outside the chamber. A specially modified (sealed and purged with nitrogen) photoflash tube inside the chamber was mounted onto a standard Ganzfeld apparatus. Visual stimuli consisted of three different intensities of blue or white light and one intensity of red light. The largest b-wave amplitude obtained in two or three trials was recorded for each intensity.

After magnification by a Grass Model P511 Amplifier, the electrical signal from the ERG electrode was recorded and stored within the memory of a Hewlett-Packard Model 3561A Signal Analyzer. Hard Copy of the ERG trace was obtained with a Hewlett-Packard Model 2671-G Graphic Printer.

Perimetry. Peripheral visual field measurements were made monocularly on the light adapted (left) eye with the right eye patched. Perimetric fields were plotted every 30° on a Rodenstock Projection Perimeter using the 1.12 mm test spot. Field luminance of the hemisphere was fixed at 0.50 log mL,

while luminance of the test spot was maintained at 2.0 log mL. All external chamber lights were turned off during the period of visual field measurement. Maintenance of proper fixation was assured throughout each period of measurement by frequent monitoring with the viewing device built into the perimeter. The stimulus was presented randomly in any of the 12 selected field locations, with each presentation being from the "not seen" to the "seen" mode. Responses to two complete sets of presentations were averaged for each visual field measurement.

Visual evoked cortical responses. The pattern reversal visual evoked cortical response (VER) was obtained with a Medical Systems Corporation Model D112 Pattern Reversal Stimulator outside the chamber projecting onto a rear projection screen inside the chamber via a viewport. The subject was seated with his eye at a distance of one meter from the screen. The signal from the scalp EEG electrodes (F_z/O_z) was magnified by a Grass P511 Amplifier and sent to a Hewlett-Packard 3561A Signal Analyzer for signal averaging and recording (2671-G Graphic Printer).

Visual acuity. Central visual acuity was measured with the test chart on a modified MacBeth illuminator stand. The subject was seated in front of the chart with his eye position maintained at a fixed distance of 35 cm from the chart surface by a restraining device which rested on the bridge of his nose and cheekbones. The chart was viewed under the illumination of the MacBeth source which provided 0.95 log lux illuminance (approximately equivalent to average daylight). Visual acuity of the left eye was measured with the right eye patched.

Accommodation. The closest distance at which the subject could accommodate was measured with a modified Adler Near-Point Rule. A fine-letter target attached to a millimeter rule was initially positioned to be in sharp focus for the left eye with the right eye patched. It was then moved slowly toward the eye while the subject actively accommodated to the decreasing distance until blurring began at the near-point. Accommodative near-point was measured as the average of at least 5 readings. All trials were performed with chamber lights on full brightness.

Pupilometry. Diameter of the left pupil was estimated to the nearest 0.5 mm by matching pupil size with a range of similar test circles on a standard chart. This determination was made with chamber lights on full brightness while the subject looked directly at the light.

Ventilation and Gas Exchange

During oxygen breathing at 2.0 ATA, inspiratory flow and pattern of ventilation were measured with a pneumotachygraph (Fleisch #4) on the inspiratory side of the gas administration

system. These measurements were supplemented with timed collections of expired gas in a large weather balloon which was then evacuated to 1.0 ATA for measurement of volume in a wet test gasometer. Mean expired CO₂ concentration was also measured at 1.0 ATA with a Datex Model CD-101 Infrared CO₂ Analyzer.

Arterial Blood Gases

Arterial blood was sampled anaerobically into precision-bored glass syringes by standard procedures. Analyses for pH, PCO₂, and PO₂ were performed in duplicate with a Corning Model 165 Blood Gas Analyzer electrode block especially adapted for use inside the chamber. Blood gas and pH measurements at 1.0 ATA were performed in duplicate with an Instrumentation Laboratory Model 1304 Blood Gas Analyzer.

Body Temperature

Rectal temperature was recorded continuously. The temperature sensor was a Yellow Springs 400 series probe with a Model 46 thermistor thermometer and a range of 35 to 45°C.

Pulmonary Function

Automated flow volume loops inside and outside the chamber were obtained with "dry sealed" spirometers (Ohio Medical Products Models 827 and 840) and Vacumetrics Inc. software. Carbon monoxide diffusing capacity of the lung was measured with a W. E. Collins Inc. Modular Lung Analyzer. Airway resistance, pulmonary compliance, and functional residual capacity were measured using a W. E. Collins Inc. Body Plethysmograph.

Cardiovascular Function

Electrocardiogram. The ECG was monitored continuously on a Siemens Corporation Model Sirecust 400 Clinical Monitor and recorded onto magnetic tape and a Holter Monitor.

Cardiac output. Cardiac stroke volume was measured with the aid of a Minnesota Impedance Cardiograph (Instrumentation For Medicine Inc. Model 304A) whose output was recorded onto a Honeywell Visicorder (906B) and onto magnetic tape. Cardiac output was calculated as the product of heart rate and stroke volume.

Blood pressure. Blood pressure was measured via an indwelling arterial catheter using a disposable blood-pressure transducer (Abbott Critical Care Systems) coupled to the Siemens Patient Monitor. The pulse waveform was recorded onto a Visicorder Oscillograph.

Orthostatic maneuver. An orthostatic maneuver was obtained at selected intervals by having the subject arise from the prone position to the standing position in a rapid but controlled maneuver. The ECG, beat-by-beat heart rate, blood pressure, and cardiac stroke volume were simultaneously recorded onto the Visicorder Oscillograph before, during, and after the orthostatic maneuver.

Statistical Analysis

Means and standard deviations for each measurement parameter and experimental condition are summarized in appendix data tables. Average values include all subjects for whom data are available. In some cases, it was not possible to obtain data for all subjects in each condition. For statistical comparisons of average values for different conditions, analyses across a range of conditions were performed with data only from the same subjects. All tests were made at the 5% level, with critical values adjusted for multiple comparisons where required.

Analysis of variance techniques were applied to all data obtained from measurements at regular intervals during intermittent oxygen exposure. Paired t-tests were performed on data obtained at 1.0 ATA before and after intermittent oxygen exposure at 2.0 ATA, and on data obtained at the start and end of the 2.0 ATA exposures.

RESULTS AND DISCUSSION

ANIMAL STUDIES

Effects of Intermittent Oxygen Exposure on Survival Time at 4.0, 2.0, and 1.5 ATA

Survival times in groups of 20 rats exposed intermittently to oxygen pressures of 4.0, 2.0, and 1.5 ATA are shown in Appendix Figures 5, 6, and 7, respectively. Mortality curves for oxygen periods of 20, 60, and 120 min, each combined with several normoxic intervals, are shown for each pressure. Mortality curves for groups of 20 or more rats exposed continuously to oxygen at each pressure are shown as dashed lines. Survival times for the intermittent exposures show cumulative oxygen time, with no indication of the cumulative duration of normoxic exposure. Results are described initially with respect to intermittent patterns having the same oxygen period (20, 60, or 120 min), and later with respect to patterns having the same oxygen:normoxic ratio.

Intermittent patterns with 20-min oxygen exposure periods. Alternation of 5-min normoxic intervals with 20-min oxygen exposure periods did not increase survival time at either 4.0 or 2.0 ATA (App. Figs. 5 and 6), but median survival time was increased by 24% for the same pattern at 1.5 ATA (App. Fig. 7). Doubling the normoxic interval to 10 min increased median survival time by 46% at 4.0 ATA, 29% at 2.0 ATA, and 64% at 1.5 ATA. Again doubling the normoxic interval to 20 min produced only a 56% increment in survival time at 4.0 ATA, but median survival time at 2.0 ATA was more than doubled (+113%). The 20:20 oxygen:normoxic pattern was not evaluated at 1.5 ATA for reasons that are given below.

Intermittent patterns with 60-min oxygen exposure periods. Combination of 60-min oxygen periods with normoxic intervals of 15 and 30 min increased median survival time, respectively, by 32% and 47% at 4.0 ATA, 18% and 39% at 2.0 ATA, and 26% and 42% at 1.5 ATA. The 60:60 oxygen:normoxic pattern, which was not evaluated at 1.5 ATA, increased survival time by 62% and 100% at 4.0 and 2.0 ATA, respectively. When 60-min oxygen periods were alternated with 180-min normoxic intervals at 4.0 ATA, survival time increased by 121%, but the same exposure pattern at 2.0 ATA allowed all 20 rats to tolerate 67 oxygen hours (3.7 x median survival time for continuous exposure) over a total time of 11 days without a single death. Electron microscopy of the lungs from 6 randomly selected rats revealed only minimal alterations of pulmonary ultrastructural constituents.

Intermittent patterns with 120-min oxygen exposure periods. When 120-min oxygen periods were alternated with 30-min normoxic intervals at 4.0 ATA, survival times for many rats were actually

shorter than those for continuous exposure. Evidently, the long oxygen exposure periods at 4.0 ATA, with only 30-min recovery periods, produced enough lung damage to cause fatal hypoxemia upon return to a normoxic atmosphere. The same program at 2.0 and 1.5 ATA increased median survival time by 8% and 19%, respectively. The 120:60 oxygen:normoxic pattern lengthened survival time by 47%, 33%, and 41% at 4.0, 2.0, and 1.5 ATA, respectively. When 120-min oxygen periods and normoxic intervals were alternated at 4.0 and 2.0 ATA, survival time was increased by 66-67%. At 1.5 ATA, however, the same intermittent exposure pattern was continued for 60 oxygen hours without a single death. The experiment was discontinued at this time, because the rats did not appear to be in a preterminal state at an exposure duration that already represented a 124% increment in median survival time.

Intermittent patterns with 1:1 oxygen:normoxic ratios. Relative increments in median survival times for the 20:20, 60:60, and 120:120 patterns at 4.0 ATA were 56%, 62%, and 66%, respectively (Appendix Figure 5). Corresponding patterns at 2.0 ATA produced relative gains of 113%, 100%, and 67%, respectively (Appendix Figure 6). The 20:20 and 60:60 patterns produced similar results at each pressure, and both patterns were more effective at 2.0 than at 4.0 ATA. Median survival time for the 120:120 pattern was at least equal to or slightly longer than that for the other 2 patterns at 4.0 ATA, but was much shorter than survival times for the other patterns at 2.0 ATA. The reduced effectiveness of survival time extension by the 120:120 pattern at 2.0 ATA was most evident among the more resistant rats.

In contrast to the 67% increment in survival time for the 120:120 pattern at 2.0 ATA, the same pattern at 1.5 ATA was terminated with no deaths at 60 oxygen hours which represented a 124% increment in survival time (Appendix Figure 7). The 20:20 and 60:60 exposure patterns were not evaluated at 1.5 ATA, because the results obtained at 2.0 ATA (Appendix Figure 6) indicated that they would extend survival time even more than the 120:120 pattern.

Intermittent patterns with 2:1 oxygen:normoxic ratios. All 3 intermittent exposure patterns whose oxygen:normoxic periods have a 2:1 ratio produced relative increments in median survival times of 46-47% at 4.0 ATA and 29-39% at 2.0 ATA (Appendix Figures 5 and 6). A similar uniformity of response to all 3 patterns was not found at 1.5 ATA, where both the 60:30 and 120:60 patterns increased survival time by about 42%, but the 20:10 pattern produced a 64% increment (Appendix Figure 7). With this single exception, the similarity of responses to the 20:10, 60:30, and 120:60 patterns suggests in principle that, within the range that was evaluated, a wide variety of exposure patterns with 2:1 ratios would provide similar extensions of survival

time. Operational application of the same principle would provide a means for selection of equally effective intermittent exposure patterns, within an appropriate range, on the basis of the shortest possible normoxic interval or the longest possible oxygen exposure period.

Intermittent patterns with 4:1 oxygen:normoxic ratios.

Responses to the intermittent exposure patterns with 4:1 oxygen:normoxic ratios at 4.0 and 2.0 ATA show that the 60:15 pattern provided the greatest extensions of median survival times at both oxygen pressures, with 32% and 18% increments at 4.0 and 2.0 ATA, respectively (Appendix Figures 5 and 6). The 20:5 pattern did not increase survival time at either pressure, while the 120:30 pattern decreased median survival time by 12% at 4.0 ATA and increased it by 8% at 2.0 ATA. The results at 4.0 and 2.0 ATA indicate that a 5-min normoxic interval is too short for significant recovery, with respect to survival time, even after an oxygen exposure of only 20 min. They also indicate that 120-min oxygen exposure periods cause toxic changes that reverse less completely, even when alternated with 30-min normoxic intervals, than those caused by exposures of 60 min or less.

In marked contrast to the results obtained at 4.0 and 2.0 ATA, all 3 patterns with an oxygen:normoxic ratio of 4:1 produced similar extensions of survival time at 1.5 ATA (Appendix Figure 7). Relative increments in median survival time, as compared with that for continuous exposure, for the 20:5, 60:15, and 120:30 intermittent exposure patterns were 24%, 26%, and 19%, respectively. These results indicate that significant recovery from 20-min oxygen exposure periods at 1.5 ATA can occur with normoxic intervals as short as 5 min, in contrast to the absence of survival time extension for the 20:5 intermittent exposure pattern at 2.0 and 4.0 ATA. Results obtained at 1.5 ATA also show that 120-min oxygen exposure periods are not too long to allow significant reversal of toxic effects during 30-min normoxic recovery intervals. Both observations are consistent with the fact that oxygen poisoning occurs more slowly at 1.5 ATA than at higher oxygen pressures.

Summary and Interpretations of Animal Data

Relationships of survival time increments to normoxic interval durations. Median survival times for all of the intermittent exposure patterns that have been evaluated to date are plotted against durations of the corresponding normoxic intervals in Appendix Figure 8. Points are grouped by oxygen pressure and duration of the oxygen exposure period for each pressure. Lines drawn through the 9 different groups of points indicate the rates at which survival time is lengthened by progressively increasing the duration of normoxia while holding the oxygen exposure constant at 20, 60, or 120 min. The slopes of the lines should also reflect the relative rates at which

toxic events are reversed upon termination of the corresponding oxygen exposure.

Rates of recovery in relation to exposure patterns.

Comparison of the slopes in Appendix Figure 8 indicates that recovery occurs most rapidly after the 20-min (short) oxygen exposures and least rapidly after the 120-min (long) exposures. It also indicates that rate of recovery for a given oxygen exposure period occurs more rapidly at a lower oxygen pressure. Although these relationships were anticipated qualitatively, the data consistency affords a clear quantitative description of the rate of recovery under each set of experimental conditions.

The slopes of the curves in Appendix Figure 8 can be used to estimate empirically the effectiveness of selected intermittent exposure patterns throughout the ranges of oxygen pressure and exposure period that were evaluated. Numerical values of the 3 slopes for each oxygen pressure are listed in Appendix Table 2 and plotted on each side of Appendix Figure 9. On the left the slopes of the curves at 1.5, 2.0, and 4.0 ATA are plotted on the ordinate against duration of the corresponding oxygen exposure period on the abscissa. On the right the slopes for 20-min, 60-min, and 120-min oxygen exposure periods are plotted on the ordinate against the corresponding oxygen pressure on the abscissa. Both sets of curves describe smooth relationships that would permit interpolations with a reasonable degree of accuracy. As an example, interpolated values at 3.0 ATA on the right-side curves are plotted on the left to provide a predicted curve for 3.0 ATA.

The empirical curves in Appendix Figure 9 are based on extension of survival time in rats by intermittent oxygen exposure at pressures of 1.5, 2.0, and 4.0 ATA. The quantitative relationships defined by these curves will not be directly applicable to man. However, the principles are, and it is considered that the analytical methods used to derive the descriptive curves from data obtained in rats will also be useful for the analysis of human data obtained in early, reversible stages of oxygen poisoning. Although the number of human intermittent oxygen exposures will necessarily be much more selective and limited than was possible in rats, the volume of pathophysiological information obtained from each exposure will be immensely greater. The inherently limited survival time data will be replaced by quantitative measurements of oxygen effects on multiple organ systems and functions. The rat data will also provide guidelines relevant to the determination of optimum durations for the alternating oxygen periods and normoxic intervals that, with appropriate adjustment, will aid in the development of optimum patterns of intermittent oxygen exposure for extension of organ-specific oxygen tolerance in man.

HUMAN STUDIES

EVALUATION OF ORGAN SPECIFIC RESPONSES TO INTERMITTENT EXPOSURE ON A 60:15 OXYGEN:NORMOXIC PATTERN AT 2.0 ATA.

Of the 8 subjects who were studied on this pattern, one had a claustrophobic reaction to breathing through a facemask in an enclosed space, and his exposure was stopped at 7.0 oxygen hours. Since this subject had a relatively short exposure with no subjective or objective manifestations of oxygen poisoning at the time of exposure termination, his measurements were not included in the overall analysis of data. The intermittent exposure of one other subject was stopped at 9.0 oxygen hours when he experienced severe nausea. Although his data were included in the average results reported for 7 subjects, primary emphasis was placed on statistical analysis and interpretation of average data for the 6 subjects who had longer exposures and developed objective pulmonary and visual manifestations of oxygen toxicity. Statistical analyses were performed on average data for fewer than 6 subjects in some cases where measurements were incomplete or technically flawed.

Exposure Duration and Symptoms

Duration of each intermittent oxygen exposure was expressed in terms of cumulative oxygen hours for comparison with the effects of the continuous exposures that were done previously in other subjects as part of Predictive Studies V. Exposure durations ranged from 9.0 to 15.0 hours for an overall average of 12.9 hours in 7 subjects. At regular intervals during exposure, each subject reviewed a list of symptoms and rated each as absent (0), mild (1+), moderate (2+), or severe (3+). Tolerable duration of exposure was primarily limited by pulmonary symptoms in 6 subjects who had a mean exposure duration of 13.6 oxygen hours (range 11.4-15.0 hours) and by severe nausea in 1 subject (9.0 hours). All but 1 of the 6 subjects who had severe pulmonary symptoms also had severe nausea prior to or just after the end of oxygen exposure. This was sometimes exacerbated in association with vomiting during the early post-exposure period.

Effects on Brain Electrical Activity

Online inspection of electroencephalographic records during intermittent oxygen exposure revealed no evident abnormalities of brain electrical activity. Signs of incipient convulsions were not expected during these exposures, and none were observed. Detailed analysis of the electroencephalographic records has not been completed.

Effects on Auditory-Vestibular Function

Auditory and vestibular functions were evaluated

comprehensively in each subject under controlled laboratory conditions before and after intermittent oxygen exposure at 2.0 ATA. The large volume of post-exposure measurements in conjunction with the requirement for performing auditory-vestibular measurements in a hospital laboratory during normal business hours made it impractical to obtain these measurements until about 24 hours after exposure termination. Although it is possible that subtle toxic effects could have reversed completely during this unavoidable delay, any functionally significant residual effects would be detected.

Auditory and vestibular functions were well maintained after the intermittent exposures. No significant shifts in hearing thresholds were revealed by either conventional or extended high frequency audiometry. Acoustic immittance data did not detect alterations in middle ear function, and auditory brainstem responses showed no abnormalities in neural transmission. Post-exposure caloric responses were also normal.

Mental Performance and Psychomotor Function

Mental performance and psychomotor function were evaluated in 7 subjects during air breathing at 1.0 ATA before and after oxygen exposure and during oxygen breathing at 2.0 ATA at the start and end of intermittent exposure. Individual and average results are summarized in Appendix Table 3. Testing of manual dexterity was technically satisfactory in only 4 of the 7 subjects.

Short term memory, manual dexterity, number facility, and general reasoning ability were all well maintained during and after intermittent oxygen exposure at 2.0 ATA. However, visual reaction time was increased in 6 of 7 subjects at the end of oxygen exposure with average values of 0.282 and 0.322 seconds at the start and end of exposure, respectively. Measurements obtained before and after oxygen exposure also reflected a slight lengthening of reaction time in all 7 subjects with average values of 0.283 and 0.336 seconds, respectively. Neither of these changes were statistically significant. However, in the 6 subjects who had the longest intermittent oxygen exposures (11.4 to 15.0 oxygen hours), the 0.047-second increment (16.1%) in visual reaction time observed at the end of oxygen exposure was statistically significant. It is possible that this barely detectable slowing of visual reaction time represented an effect of fatigue rather than a specific effect of oxygen toxicity.

Effects on Visual Function

Measurements of visual function that were obtained before, during, and after intermittent oxygen exposure at 2.0 ATA included visual acuity, nearpoint accommodation, pupilometry, visual evoked cortical responses, visual fields, and retinal

electrical activity. All of these parameters were measured during air breathing at 1.0 ATA before and after the intermittent oxygen exposure and during the first and last hours of oxygen exposure at 2.0 ATA. Visual field area and the electroretinogram (ERG) b-wave amplitude were also measured at regular intervals during intermittent oxygen exposure as primary indices of toxic effects on visual function.

With few exceptions, the effects of intermittent oxygen exposure at 2.0 ATA on visual function were qualitatively similar to the effects observed previously in the continuous oxygen exposures of Predictive Studies V (5,12). Average measurements of visual responses to intermittent oxygen exposure are summarized in Appendix Tables 4-6. Visual acuity, nearpoint accommodation, and pupil diameter were not detectably affected by intermittent oxygen exposure at 2.0 ATA (Appendix Table 4). In contrast to previous observation of no change during and after continuous oxygen exposure at 2.0 ATA, however, latency of the visual evoked cortical response was significantly increased at the end of intermittent oxygen exposure by an average value of 5.79 milliseconds (5.1%).

Average changes in visual field area during and after intermittent oxygen exposure at 2.0 ATA are summarized in Appendix Table 5. In the 6 subjects who had the longest oxygen exposures, average visual field area was significantly reduced by 13.9% at an exposure duration 11.2 oxygen hours. It then recovered partially to be reduced by 8.4% during the last hour of exposure. An equal decrement during the early post-exposure period was not statistically significant.

Electroretinographic responses (b-wave amplitude) to 3 different light intensities are summarized in Appendix Table 6. With few exceptions, average retinal responses to all 3 intensities were significantly reduced during the last hour of oxygen exposure and were further reduced during the early post-exposure period. The only 2 values that were not significantly reduced were the post-exposure response to the intermediate light intensity (N=6) and the end-exposure response to the brightest light flash (N=6). Average percent decrements for the 3 combined light intensities in the 6 subjects who had the longest intermittent oxygen exposures are shown in Appendix Figure 10 along with comparable average responses for 7 other subjects who were previously exposed continuously to oxygen at 2.0 ATA in Predictive Studies V.

The average ERG b-wave amplitude during continuous exposure was not detectably altered for the first 4 hours and then decreased nearly linearly to reach an average decrement of 39.4% after 9.4 hours of exposure. During intermittent oxygen exposure, average b-wave decrements of 8.2% at 5.4 oxygen hours, 8.5% at 9.4 oxygen hours, followed by a progressive decline to

31.9% at 13.6 oxygen hours, define a curve that appears initially to be superimposed on the curve for continuous exposure, then shifts abruptly to the right to fall in parallel with the continuous exposure curve.

Rate and Pattern of Pulmonary Ventilation

As potential indices of toxic effects on pulmonary ventilation and ventilatory control, rate and pattern of ventilation were measured before, during, and after intermittent oxygen exposure at 2.0 ATA. Measurements of ventilation along with rate of CO₂ elimination were obtained by collection of expired gas during air breathing at 1.0 ATA before and after intermittent oxygen exposure and at regular intervals during the 2.0 ATA oxygen exposure. Average values obtained in all 7 subjects and in the 6 subjects who were exposed for 11.4 to 15.0 oxygen hours are summarized in Appendix Table 7. Average values for fewer than 6 subjects are also indicated where complete data are not available. Some of the average values for the various combinations of subjects that are cited below are not included in Appendix Table 7.

In the transition from breathing air at 1.0 ATA to breathing oxygen at 2.0 ATA, expiratory minute volume increased significantly from 6.78 to 9.77 L/min (N=5). This well defined stimulatory effect of acute hyperoxia on ventilation is caused by central accumulation of CO₂ secondary to an oxygen-induced alteration in blood CO₂ transport (3,7). The same 5 subjects had a decrease in expiratory minute volume from 11.18 to 8.47 L/min during the reverse transition from oxygen breathing at 2.0 ATA to air breathing at 1.0 ATA. The ventilatory changes observed at the start and end of oxygen exposure were associated with reciprocal changes in end-tidal PCO₂. Average PCO₂ (N=7) decreased significantly from 40.8 mm Hg during air breathing at 1.0 ATA to 33.6 mm Hg at the start of the 2.0 ATA oxygen exposure. In the reverse transition at the end of oxygen exposure, end-tidal PCO₂ (N=6) increased from 30.8 to 36.2 mm Hg.

An increased frequency of breathing with a related reduction in tidal volume was found near the end of prolonged, continuous oxygen exposures at 1.5 or 2.0 ATA (7,13). Since this response occurred concurrently with pulmonary symptoms of at least moderate severity, it may have represented a conscious or reflex effort to avoid chest pain by using a shallow, tachypneic breathing pattern.

The data summarized in Appendix Table 7 indicate that prolonged, intermittent oxygen exposure at 2.0 ATA provoked a similar response. Average respiratory rate in the 6 subjects who had the longest oxygen exposures increased significantly from 15.7 to 20.1 breaths/min at the start and end of oxygen exposure, respectively. The associated reduction in tidal volume from

0.56 to 0.51 L was not significant. Although the concurrent change in expiratory minute volume from 9.54 to 11.17 L/min was not statistically significant, the preceding value of 11.10 L/min at 11.6 oxygen hours was significantly elevated by analysis of variance. End-tidal PCO₂ also decreased significantly from 33.9 mm Hg at the start to 30.1 mm Hg at the end of oxygen exposure.

Effects on Pulmonary Function

Rate of development of pulmonary oxygen poisoning during intermittent oxygen exposure at 2.0 ATA was monitored subjectively at regular intervals by repeated surveys of pulmonary symptoms. Each symptom survey included individual ratings of cough, chest pain, chest tightness, and shortness of breath as absent (0), mild (1+), moderate (2+), or severe (3+). Average ratings of all 4 pulmonary symptoms were combined at each exposure interval for the 6 subjects whose exposures were long enough to reach pulmonary limits. These overall "pulmonary symptom" ratings are plotted against exposure duration in Appendix Figure 11 to describe rate of development of pulmonary symptoms during intermittent exposure at 2.0 ATA on a 60:15 oxygen:normoxic pattern. For comparison with this curve, Appendix Figure 11 also contains a similar curve obtained previously in this laboratory for continuous oxygen exposure at 2.0 ATA (6,14) and a curve obtained by Hendricks et al (1) for intermittent exposure at 2.0 ATA on a 20:5 oxygen:normoxic pattern. Both patterns of intermittent oxygen exposure delay the development of pulmonary symptoms by degrees that are remarkably similar given the subjective nature of the available information.

Rate of decrease in vital capacity. Flow-volume loops were performed at regular intervals during intermittent oxygen exposure at 2.0 ATA to monitor toxic effects on pulmonary mechanical function. Average values for selected lung volumes and flow rates are summarized in Appendix Table 8. Of the lung volumes and flow rates that can be obtained from a flow-volume loop, vital capacity proved to be a useful index of pulmonary oxygen poisoning during intermittent exposure (1), as it had previously during continuous oxygen exposure (13). Average vital capacity data for the 6 subjects who had the longest intermittent exposures are plotted in Appendix Figure 12 along with average curves obtained previously for continuous exposure in this laboratory (14) and for intermittent exposure on a 20:5 pattern by Hendricks et al (1). Both curves for intermittent exposure reflect increments in pulmonary oxygen tolerance, but the 20:5 exposure pattern appears to be more effective.

Individual vital capacity data for the 6 subjects exposed for 11.4 to 15.0 oxygen hours on the 60:15 intermittent exposure pattern are superimposed on the curves for continuous oxygen exposure and intermittent exposure on the 20:5 pattern in Appendix Figure 13. The data show that rates of decrease in

vital capacity for 4 subjects on the 60:15 pattern are similar to the average curve for the 20:5 intermittent exposure pattern, while rates of vital capacity decrement for the other 2 subjects are closer to the average curve for continuous oxygen exposure. These similarities are even more evident in Appendix Figure 14 where the average curve for the 4 subjects who had relatively slow rates of decrease in vital capacity on the 60:15 intermittent exposure pattern is nearly superimposed on the average curve for the 20:5 exposure pattern, while the average curve for the other 2 subjects is much closer to the average curve for continuous oxygen exposure.

Post-exposure evaluation of pulmonary function. In addition to measuring lung volumes and flow rates at regular intervals during intermittent oxygen exposure at 2.0 ATA, extensive evaluations of pulmonary function were performed at 1.0 ATA before and after the 2.0 ATA intermittent oxygen exposure. Average results of these measurements are summarized in Appendix Table 9. Average values are given for all 7 subjects and for the 6 subjects who had the longest oxygen exposures.

Separate measurements of vital capacity as part of a flow-volume loop (FVC) or as an independently performed slowly delivered exhalation (SVC) are in good agreement. Average FVC and SVC decrements in the 6 subjects who reached pulmonary limits of exposure are both 0.59 L (representing 11.3% and 11.1%, respectively, of the corresponding control values). This measurement, obtained about 3-4 hours post-exposure, reflects partial recovery from the 14.7% decrement that was present at the end of oxygen exposure (Appendix Figure 12). Concurrent measurements of inspiratory capacity (IC) and expiratory reserve volume (ERV) (Appendix Table 9) show that the vital capacity decrement is contained within the inspiratory component of this lung volume, in agreement with previous observations obtained after continuous oxygen exposure at 2.0 ATA (13).

Lung expiratory function and compliance. Many indices of lung expiratory function were decreased after intermittent oxygen exposure at 2.0 ATA (Appendix Tables 8 and 9). During the early post-exposure period, average values of the one-second forced expired volume (FEV₁) and peak expiratory flow rate (PEFR) were significantly reduced by 0.52 L (11.6%) and 1.55 L/sec (15.0%), respectively. Although maximal mid-expiratory flow rate (FEF₂₅₋₇₅) was reduced in 5 of the 6 subjects, the average decrement (0.67 L/sec or 10.9%) was not statistically significant.

In agreement with previous observations after continuous oxygen exposure (14,15), airway resistance (R_{aw}) was not increased after intermittent exposure at 2.0 ATA (Appendix Table 9). Since the measured value of R_{aw} is determined primarily by resistance to flow through the larger, proximal airways, the

impairment of lung expiratory function that has been found repeatedly after either intermittent or continuous oxygen exposure at 2.0 ATA is apparently caused by increased resistance to flow through the smaller, peripheral airways (6,16).

In the 6 subjects who had the longest intermittent oxygen exposures, the average value of specific lung compliance ($C_{L/FRC}$) was significantly reduced by 0.029 L/cm H₂O/L (20.2%) during the early post-exposure period. At the same time in 5 of the same subjects, the average value for density dependence of expiratory flow rate ($\Delta\dot{V}_{max50}$) was reduced by 10.8%, but this change was not statistically significant. Both of these parameters were reduced significantly after continuous oxygen exposure at 2.0 ATA (14).

Lung diffusing capacity and arterial oxygenation. The average value for lung carbon monoxide diffusing capacity (DL_{CO}) during the early post-exposure period was nearly identical to the pre-exposure control value (Appendix Table 9). However, DL_{CO} fell progressively over the next 2 days for average decrements of 8.1% on post-exposure day 1 and a statistically significant 11.7% on post-exposure day 2 (Data not shown in Table). A similar continuation of the post-exposure reduction in DL_{CO} was observed after continuous oxygen exposure at 2.0 ATA for an average time of 9.4 hours (17).

Effects of intermittent oxygen exposure at 2.0 ATA on selected parameters of arterial oxygenation and acid-base state are summarized in Appendix Table 10. Average alveolar-arterial oxygen differences (N=4) measured at rest during the first and last hours of oxygen breathing at 2.0 ATA were 45 and 59 mm Hg, respectively. Alveolar-arterial oxygen differences were also measured at rest and during exercise while breathing air at 1.0 ATA before and after intermittent exposure at 2.0 ATA. Average pre-exposure values at rest and during exercise (N=5) at a mean oxygen uptake of 1.34 L/min were 1.5 and 7.8 mm Hg, respectively. Corresponding post-exposure values were 9.8 and 14.4 mm Hg. None of the observed increments in alveolar-arterial oxygen differences were statistically significant.

Although arterial oxygenation was not significantly altered during late exposure or in the early post-exposure period, there were statistically significant changes in several indices of arterial acid-base state. These changes included a small but statistically significant decrease in arterial pH during oxygen exposure, significant reductions in arterial PCO_2 and $[HCO_3^-]$ at rest while breathing air during the early post-exposure period, and reduction in arterial PCO_2 with concurrent elevations in arterial pH and alveolar PO_2 during the subsequent exercise period. These changes are generally consistent with loss of bicarbonate during the prolonged intermittent oxygen exposure and with mild hyperventilation during the early post-exposure period.

Effects on Respiratory and Skeletal Muscle Strength

Average values of maximum inspiratory and expiratory pressures and maximum handgrip strength are summarized in Appendix Table 11. In the 6 subjects who had the longest intermittent oxygen exposures, maximum inspiratory pressure during the early post-exposure period was reduced by 30.6 cm H₂O (21.2%) at residual volume and by 22.7 cm H₂O (17.9%) at functional residual capacity. Concurrent values of maximum expiratory pressure were reduced by 22.2 cm H₂O (16.6%) at total lung capacity and by 34.6 cm H₂O (26.3%) at functional residual capacity. None of the observed changes in maximum respiratory pressures were statistically significant.

Maximum handgrip strength was reduced by only 0.8 Kg (1.5%) during the early post-exposure period, and the tolerable duration for sustaining 80% of maximum handgrip power, measured as an index of endurance, was reduced by 8.8 seconds (24.9%). Neither of these changes were statistically significant.

Effects on Cardiovascular Function and Body Temperature

Cardiovascular parameters measured before, during, and after intermittent oxygen exposure at 2.0 ATA include heart rate, stroke volume, cardiac output, mean arterial blood pressure, and systemic vascular resistance. Rectal temperature was also measured as an index of deep body temperature. Individual and average values are summarized in Appendix Table 12. Average values are shown for all 7 subjects and for the 6 subjects who had the longest exposures.

Heart rate decreased in all 7 subjects at the start of oxygen exposure with an average decrement from 56.7 to 48.4 beats/min. Stroke volume changed less consistently with an average increment of only 137.0 to 141.1 ml. Average cardiac output decreased from 7.75 to 6.89 L/min, but this change was not statistically significant. In the 6 subjects who had the longest intermittent oxygen exposures, average heart rate increased significantly from 48.3 beats/min at the start of exposure to 55.2 and 55.3 beats/min at 10.7 and 11.7 oxygen hours, respectively, and to 59.0 beats/min during the last exposure hour. The increased heart rate was associated with a significant reduction in stroke volume from 133.5 to 105.7 ml. A similar initial reduction and later acceleration of heart rate was found during continuous oxygen exposure at 2.0 ATA (8).

Mean arterial blood pressure and systemic vascular resistance did not change significantly at the start of oxygen exposure and were not consistently altered during the course of the exposure. There was a small but statistically significant increase in deep body temperature from a pre-exposure value of 36.7°C to 37.0°C (N=6) during the early post-exposure period.

In summary, the cardiovascular responses to intermittent oxygen exposure at 2.0 ATA were generally consistent with previously observed responses to continuous oxygen exposure at the same pressure (8), with no prominent pathophysiologic effects on cardiovascular function.

EVALUATION OF ORGAN SPECIFIC RESPONSES TO INTERMITTENT EXPOSURE ON A 30:30 OXYGEN:NORMOXIC PATTERN AT 2.0 ATA.

During the final phase of this Program, 6 intermittent oxygen exposures with the 30:30 oxygen:normoxic sequence were completed at 2.0 ATA. The total number of subjects was limited by the difficulty encountered in recruiting student volunteers for an experiment that required 5 consecutive days for pre-exposure, exposure, and post-exposure measurements, with additional days for medical evaluation, training, and follow-up measurements. Average values and statistical analyses of the data for the measured organ specific responses to the 30:30 oxygen:normoxic intermittent exposure pattern are summarized in Appendix Tables 13 to 22.

Exposure Duration and Symptoms

Of the 6 intermittent exposures that were completed on the 30:30 pattern, 4 were continued for the planned duration of 15.0 oxygen hours, and the other 2 were stopped at 13.0 hours. As was done previously for the continuous and 60:15 intermittent exposure series, each subject reviewed a list of symptoms at regular intervals and rated each symptom as absent (0), mild (1+), moderate (2+), or severe (3+). Although symptoms remained generally mild, the first exposure was stopped at 13.0 oxygen hours when the subject appeared to be developing prominent decrements in visual and pulmonary function. The last exposure was also stopped at 13.0 oxygen hours when the subject became extremely anxious in association with chest tightness and shortness of breath. One subject vomited several times during the early post-exposure period.

Effects on Brain Electrical Activity

As observed previously during the continuous and 60:15 intermittent exposure series, online inspection of electroencephalographic records revealed no evident abnormalities of brain electrical activity.

Effects on Auditory-Vestibular Function

In agreement with previous findings after both continuous and intermittent oxygen exposures, significant shifts in hearing thresholds were not detected by either conventional or extended high frequency audiometry. Post-exposure evaluations of middle ear function by acoustic immittance and auditory brainstem

responses as an index of neural transmission revealed no abnormalities. Post-exposure caloric responses were also normal.

Mental Performance and Psychomotor Function

Average results of mental performance and psychomotor function evaluations are summarized in Appendix Table 13. Average scores for short term memory ability and number facility were generally maintained or increased slightly at the end of the intermittent oxygen exposure or during the early post-exposure period. Manual dexterity scores were significantly reduced post-exposure, with average pre and post-exposure values of 62.7 and 49.2 (-21.5%), respectively. Average visual reaction time was reduced by 0.013 seconds at the end of oxygen exposure and increased by 0.034 seconds during the early post-exposure period. Neither of these changes were statistically significant.

Effects on Visual Function

Average measurements of visual responses to intermittent oxygen exposure on the 30:30 sequence are summarized in Appendix Tables 14-16. Average values for visual evoked cortical responses, nearpoint accommodation, and pupil diameter were similar before, during, and after intermittent oxygen exposure (Appendix Table 14). Except for a minor change from 20/25 to 20/30 in one subject, visual acuities were identical before, during, and after exposure.

Average values of peripheral visual field area measured before, during, and after intermittent oxygen exposure are summarized in Appendix Table 15. With respect to the control measurement at the start of oxygen exposure, average values were reduced by 5.5% at 8.0 oxygen hours, increased by 2.5% at 10.0 hours, reduced again by 6.4% at 13.0 hours, and decreased by 5.3% at the end of oxygen exposure. With respect to the pre-exposure control value, average visual field area was increased by 3.1% during the early post-exposure period. None of the observed changes in visual field area were statistically significant. In contrast, average visual field areas in the 6 subjects who were exposed on the 60:15 oxygen:normoxic sequence were significantly reduced by 13.9% and 8.4%, respectively, at 11.2 and 13.6 oxygen hours (Appendix Table 5).

Average electroretinographic responses (b-wave amplitude) to 3 different light intensities are summarized in Appendix Table 16. With respect to the control measurement at the start of oxygen exposure, average responses to the lowest light intensity fell to the lowest value (-15.6%) at 8.0 oxygen hours, then rose to -1.3% at 12.0 hours, decreased to -6.3% at 13.0 hours, and rose to -3.5% at the end of the exposure. Corresponding responses to the intermediate intensity also reached the lowest value (-26.8%) at 8.0 hours, followed by a partial recovery to an

average decrement of 9.1% at the end of oxygen exposure. In agreement with observed responses to the two lower intensities, average responses to the brightest light intensity fell to the lowest value (-14.3%) at 8.0 oxygen hours. Thereafter, these responses recovered fully to reach an average increment of 4.0% at the end of intermittent oxygen exposure. With respect to pre-exposure control values, average changes during the early post-exposure period were -11.3%, -11.8%, and +5.9%, respectively, for the lowest, intermediate, and highest light intensities. Of all the observed changes in ERG b-wave amplitude during and after intermittent oxygen exposure, only the 26.8% decrement in response to the intermediate light intensity at 8.0 oxygen hours and the 9.1% decrement in response to the same light intensity at the end of oxygen exposure were statistically significant.

Average percent decrements in ERG b-wave amplitude calculated from individual average responses to all 3 light intensities are shown in Appendix Figure 15 for all 6 subjects exposed on the 30:30 oxygen:normoxic sequence, along with corresponding data for 7 subjects exposed continuously and 6 subjects exposed intermittently on the 60:15 sequence (Shown previously in Appendix Figure 10). With respect to the initial control value, average results for the 6 subjects on the 30:30 sequence were essentially unchanged through 6.0 oxygen hours, fell abruptly to an average decrement of 19.5% at 8.0 hours, and then recovered progressively to reach an average decrement of only 3.3% at the end of the intermittent exposure. Progressive recovery of ERG b-wave amplitude during the second half of the intermittent exposure on the 30:30 sequence contrasted sharply with the concurrent progressive decrements in b-wave amplitude observed during both continuous oxygen exposure and intermittent exposure on the 60:15 sequence.

Rate and Pattern of Pulmonary Ventilation

Average measurements of ventilatory responses to intermittent oxygen exposure on the 30:30 sequence are summarized in Appendix Table 17. As noted previously at the start of either continuous or intermittent oxygen exposure, expiratory minute volume increased significantly during the transition from breathing air at 1.0 ATA to breathing oxygen at 2.0 ATA. Both the average pre-exposure value of 7.30 L/min and the initial exposure value of 10.38 L/min were used as control values for subsequent measurements at 2.0 or 1.0 ATA. With respect to these control values, there were no significant changes in expiratory minute volume during either the intermittent oxygen exposure at 2.0 ATA or the early post-exposure period at 1.0 ATA. Similarly, there were no significant changes in respiratory rate, tidal volume, or rate of CO₂ elimination during the exposure or post-exposure periods.

Average end-tidal PCO_2 , after decreasing significantly from a pre-exposure value of 40.2 mm Hg to 33.8 mm Hg at the start of exposure, increased significantly to 36.2 mm Hg at 7.6 oxygen hours. There were no other significant changes in end-tidal PCO_2 except for the expected elevation from 33.2 to 37.2 mm Hg during the reverse transition from oxygen breathing at 2.0 ATA to air breathing at 1.0 ATA. The observed elevation from 33.8 mm Hg at the start of intermittent exposure to 36.2 mm Hg at 7.6 oxygen hours may have been related to the fact that this measurement was made at 0300 to 0400 hours when the subjects would normally have been asleep. A reduced ventilatory response to metabolically produced CO_2 with a reciprocal elevation in arterial and end-tidal PCO_2 has been observed during sleep (18) and in normal men who were awakened intermittently during the night (19).

Effects on Pulmonary Function

Average pulmonary symptom ratings for the 6 subjects who were exposed on the 30:30 oxygen:normoxic sequence are plotted against exposure duration in Appendix Figure 16 along with the pulmonary symptom curves shown previously (Appendix Figure 11) for continuous exposure and for intermittent exposure on the 60:15 sequence. As expected, pulmonary symptoms developed more slowly and were less severe on the 30:30 sequence than for the previous intermittent exposures on the 60:15 sequence. Average symptom ratings at the end of each of the 3 exposure series were 1.0 at 14.3 oxygen hours on the 30:30 sequence, 2.0 at 13.6 oxygen hours on the 60:15 sequence, and 2.1 at 9.2 hours of continuous exposure.

Rate of decrease in vital capacity. Average values for selected lung volumes and flow rates measured before, during, and after intermittent exposure on the 30:30 sequence are summarized in Appendix Table 18. Average percent changes in vital capacity were selected for comparison with similar data obtained during continuous exposure (N=16) and intermittent exposure on the 60:15 sequence (N=6) (Appendix Figure 17). Average vital capacity decrements for the 6 subjects exposed intermittently on the 30:30 sequence initially were nearly superimposed on the curve for continuous exposure to reach an average decrement of 6.0% at 8.0 oxygen hours, then remained essentially constant, crossing the curve for intermittent exposure on the 60:15 sequence at 11.1 hours to end at an average decrement of 6.1% at 14.3 oxygen hours. Individual changes in vital capacity at the end of oxygen exposure varied from -9.2% to +1.4% of the initial control value. All of the changes in vital capacity observed from 8.0 to 14.3 oxygen hours were statistically significant. Although intermittent exposure on the 30:30 sequence allowed nearly 15 hours of oxygen breathing at 2.0 ATA with a relatively small change in vital capacity, as predicted, the observation of vital capacity decrements that initially exceeded those found previously for the 60:15 sequence was not expected.

Post-exposure evaluation of pulmonary function. Average values for selected components of extensive evaluations of pulmonary function that were performed before and after intermittent oxygen exposure at 2.0 ATA are summarized in Appendix Table 19. The average changes were generally smaller than those found after intermittent exposure on the 60:15 sequence (Appendix Table 9) with only a few exceptions. One of the exceptions was a consistent reduction in specific lung compliance in all 6 subjects for an average decrement of 23.8% after intermittent exposure on the 30:30 sequence. This statistically significant change was very similar to the corresponding value of 20.2% found after exposure on the 60:15 sequence.

Lung carbon monoxide diffusing capacity was also reduced by a small, but statistically significant, average change of -4.9% during the early post-exposure period, with subsequent, significant changes of -11.3%, -11.3%, and -12.0% on post-exposure days 1, 2, and 3, respectively. After intermittent exposure on the 60:15 sequence, lung carbon monoxide diffusing capacity was not changed (+0.6%) during the early post-exposure period, with average changes of -8.1% on post-exposure day 1 and a statistically significant -11.7% on post-exposure day 2.

Average values for selected parameters of arterial oxygenation and acid-base state measured before, during, and after intermittent exposure on the 30:30 sequence are summarized in Appendix Table 20. None of the observed changes were statistically significant, and most of the average values measured pre-exposure and during the first 30 minutes of oxygen breathing were similar to corresponding values measured during the last 30 minutes of exposure and during the early post-exposure period.

Effects on Respiratory and Skeletal Muscle Strength

Average values of maximum inspiratory and expiratory pressures and maximum handgrip strength are summarized in Appendix Table 21. Maximum inspiratory pressure during the early post-exposure period was reduced by 19.5 cm H₂O (13.3%) at residual volume and by 4.0 cm H₂O (3.4%) at functional residual capacity. Concurrent values of maximum expiratory pressure were reduced by 24.5 cm H₂O (17.7%) at total lung capacity and by 15.3 cm H₂O (11.6%) at functional residual capacity. None of the observed changes in maximum respiratory pressures were statistically significant.

Maximum handgrip strength was reduced by 3.6 Kg (7.2%) during the early post-exposure period, and the tolerable duration for sustaining 80% of maximum handgrip power, measured as an index of endurance, was reduced by 7.4 seconds (17.3%). Neither of these changes were statistically significant.

Effects on Cardiovascular Function and Body Temperature

Average values of heart rate, stroke volume, cardiac output, mean arterial blood pressure, systemic vascular resistance, and deep body temperature measured before, during, and after intermittent oxygen exposure at 2.0 ATA are summarized in Appendix Table 22. Average heart rate increased significantly from 53.8 to 62.2 beats/min at the start and end of intermittent oxygen exposure, respectively. A concurrent reduction in average stroke volume from 102.6 to 82.2 ml was not statistically significant. There were no significant changes in cardiac output, mean arterial blood pressure, or systemic vascular resistance. Average deep body temperature decreased significantly from 37.0°C at the start of oxygen exposure to 36.6°C at 8.0 oxygen hours. It then increased during the remainder of the intermittent exposure to reach an average value of 37.3°C during the early post-exposure period that was significantly larger than the pre-exposure value of 37.0°C.

In summary, the cardiovascular responses to intermittent oxygen exposure at 2.0 ATA on the 30:30 pattern were generally consistent with previously observed responses to both intermittent exposure on the 60:15 pattern (Appendix Table 12) and to continuous oxygen exposure at the same pressure (8), with no prominent pathophysiologic effects on cardiovascular function.

INTERPRETATION AND RELEVANCE OF RESULTS

In agreement with results of the previous continuous oxygen exposures at 2.0 ATA in Predictive Studies V, intermittent oxygen exposure at 2.0 ATA on either the 60:15 or 30:30 oxygen:normoxic sequence had little or no effect on brain electrical activity, auditory and vestibular function, mental performance, and psychomotor function. Observed changes in the rate and pattern of pulmonary ventilation were consistent with previously documented physiological responses to hyperoxia (3), except for an elevation in respiratory rate that was statistically significant at the end of intermittent oxygen exposure on the 60:15 sequence. Cardiovascular responses to intermittent oxygen exposure were also consistent with previously observed physiological responses, except that average heart rates were significantly increased by about 22% at the end of exposure on the 60:15 pattern and by about 15% on the 30:30 pattern. Similar increments in respiratory and heart rates also occurred during prolonged, continuous oxygen exposure at 2.0 ATA (7,8).

The most prominent toxic effects of intermittent oxygen exposure at 2.0 ATA, again in agreement with results of the previous continuous exposures, were manifested as significant alterations in specific aspects of visual function (retinal electrical activity and peripheral vision) and in several indices of pulmonary function. The physiological and operational relevance of the observed changes will be emphasized in the remainder of this discussion.

Comparative Rates of Development of Visual and Pulmonary Effects of Oxygen Toxicity during Continuous and Intermittent Oxygen Exposure at 2.0 ATA

Rates of decline in ERG b-wave amplitude and forced vital capacity in the same 7 subjects exposed continuously to oxygen at 2.0 ATA are shown in Appendix Figure 18. Average decrements in ERG b-wave start earlier and are larger than corresponding FVC decrements. Since the lung is exposed to a higher oxygen pressure than any other organ, these data indicate that retinal bipolar and glial cells, which produce the ERG b-wave, are more sensitive to oxygen toxicity than the pulmonary cells that are responsible for the still poorly understood fall in vital capacity. Previous in vitro studies have also shown that respiration of rat brain slices is inactivated before that of lung slices during exposure to the same oxygen pressure (20-22).

Our data show that ERG b-wave amplitude is decreased prominently, along with a smaller but statistically significant reduction in peripheral visual field area (12), before the occurrence of convulsions or detectable decrements in other CNS functions during continuous oxygen exposure at 2.0 ATA. These results appear to indicate that retinal function, by virtue of

specific sensitivities of retinal cells and/or the oxygen dose to which the retina is exposed, is more susceptible to oxygen poisoning than other critical CNS functions.

During intermittent oxygen exposure at 2.0 ATA on the 60:15 oxygen:normoxic sequence, average measurements in 6 subjects again show that decrease in ERG b-wave amplitude precedes the fall in vital capacity (Appendix Figure 19). During intermittent exposure, however, changes in both ERG b-wave amplitude and vital capacity are delayed and smaller than the corresponding changes previously observed during continuous exposure.

Average changes in ERG b-wave amplitude and FVC are shown in Appendix Figure 20 for the 6 subjects who were intermittently exposed on the 30:30 oxygen:normoxic sequence. The pattern of results found in this series of exposures differs significantly from that found during either continuous exposure or the 60:15 intermittent exposure series. In contrast to the progressive decrements in both FVC and ERG b-wave amplitude that were observed previously, average FVC on the 30:30 sequence reached an average decrement of 6.0% at 8.0 oxygen hours and then essentially plateaued during the remainder of the exposure, while the ERG b-wave amplitude actually recovered to an average decrement of 3.3% at the end of exposure after reaching a maximal decrement of 19.5% at 8.0 oxygen hours. Possible mechanisms for the apparent partial recovery during continued intermittent exposure will be discussed below.

Extension of Oxygen Tolerance on the 60:15 Oxygen:Normoxic Sequence

Average changes in both ERG b-wave amplitude and FVC for 7 subjects exposed continuously to oxygen at 2.0 ATA and for the 6 subjects exposed intermittently on the 60:15 sequence are shown in Appendix Figure 21. The data reflect increased tolerances to both visual and pulmonary effects of oxygen toxicity in the subjects who were exposed intermittently. Although the horizontal distances or exposure durations between the curves are roughly similar for corresponding effects, it is not likely that degrees of oxygen tolerance for a single pattern of intermittent exposure are truly equal for the observed visual and pulmonary effects of oxygen toxicity.

Local differences in blood flow and metabolic rate cause the oxygen tensions to vary widely among different tissues and organs for any level of inspired PO_2 (3,23). In addition to local differences in oxygen dose, the nature and capacity of antioxidant defenses are also likely to vary at different organ, tissue, or even cellular sites. For example, results of the previous continuous oxygen exposures of Predictive Studies V have shown that ERG b-wave amplitude and peripheral visual field area, both visual functions that originate in the retina, are impaired

at different rates during oxygen exposure at both 3.0 and 2.0 ATA (12).

During intermittent exposure to oxygen at any ambient pressure, the cyclical insertion of recovery periods imposes another level of complexity by superimposing the influences of varying rates of recovery in different organ systems and from different effects of oxygen toxicity (23). Average data from the 30:30 intermittent exposure series (Appendix Figure 20) indicates the possibility of yet another level of complexity related to stabilization or actual reversal of some toxic effects while the oxygen exposure is still in progress. For all of these reasons, degrees of oxygen tolerance extension for a single pattern of intermittent exposure at a given oxygen pressure are likely to vary for different toxic effects and among different organ systems (23).

Extension of Oxygen Tolerance on the 30:30 Oxygen:Normoxic Sequence

With respect to the 60:15 oxygen:normoxic sequence, the 30:30 sequence halves the toxic oxygen period and doubles the normoxic recovery interval. On the basis of general principles of oxygen tolerance extension by intermittent exposure, and in agreement with results of the 60:15 exposure sequence and the extensive animal studies that were completed previously under this Program, it was anticipated that visual and pulmonary effects of oxygen toxicity would be undetectable or small in magnitude throughout the 15.0 oxygen exposure hours that were planned for the 30:30 sequence (total exposure duration of 29.5 hours).

During the intermittent exposure of the first subject to be studied on the 30:30 protocol, it was therefore surprising when both ERG b-wave amplitude and vital capacity decreased at faster rates than those found during the previously completed 60:15 exposure sequence. This unexpected observation led to the decision to terminate the first exposure of the new sequence at 13.0 oxygen hours rather than the planned 15.0 hours. Since this decision had to be made in advance in order to complete all of the planned measurements, it could not be readily changed when the final exposure measurements showed partial reversals of both visual and pulmonary effects of oxygen toxicity. However, the next 4 intermittent exposures were all continued for the full 15.0 oxygen exposure hours. As stated previously, the last exposure was also stopped at 13.0 oxygen hours when the subject became extremely anxious in association with chest tightness and dyspnea.

Although the biochemical mechanisms responsible for extension of oxygen tolerance by systematic alternation of oxygen and normoxic exposure periods are not known, it is likely that

partial reversals of toxic effects during the normoxic recovery periods play a major role. The animal studies performed during the early years of this Program showed that essentially complete recovery from each successive oxygen exposure period could be provided by selecting appropriate lengths for the alternating oxygen exposure and normoxic recovery periods. However, the use of survival time as an index of oxygen tolerance, although useful for statistical validation of effective intermittent exposure patterns in large numbers of rats, provided limited insights into possible mechanisms for the observed benefits.

The observation that initial decrements in FVC and ERG b-wave amplitude were stabilized or partially reversed during continued intermittent oxygen exposure on the 30:30 sequence (Appendix Figures 15 and 17) indicates that during the final hours of exposure the degree of recovery that occurred during each normoxic interval must have equalled or exceeded the cumulative toxic effects caused by the preceding oxygen period for both visual and pulmonary manifestations of oxygen toxicity. These apparently enhanced capacities for recovery from oxygen poisoning were not evident during the first 8 to 10 hours of exposure (expressed as cumulative oxygen time by omitting the intermittent periods of normoxia) when the degrees of visual and pulmonary oxygen tolerance extension provided by the 60:15 exposure sequence were overtly equal to or exceeded those provided by the 30:30 sequence.

It is important to recognize that the decrements in visual and pulmonary function that were measured during the 30:30 intermittent exposure pattern exceeded those associated with the 60:15 pattern only when both sets of data are plotted against cumulative oxygen hours of exposure. When the observed results are plotted against duration of exposure expressed as real time by including the cumulative normoxic intervals, the average decrements in visual and pulmonary function associated with the 30:30 pattern are smaller than the corresponding decrements for the 60:15 pattern at any selected duration of total exposure time (Appendix Figures 22 and 23). This is as expected, because it is inconceivable that the 30:30 intermittent exposure pattern, which halves the oxygen exposure period and doubles the normoxic recovery period with respect to the 60:15 pattern, could produce greater degrees of oxygen poisoning at any duration of real time.

Possible Mechanisms for Oxygen Tolerance Extension during Intermittent Exposure

It is now well established that exposure to hyperoxia increases the rates of production of active species that are concurrently opposed by a variety of antioxidant defenses (24,25). At a sufficiently high oxygen pressure and/or for a sufficiently prolonged duration of exposure, oxidant damage to cells and tissues occurs when antioxidant defenses are

overwhelmed. Periodic interruption of oxygen exposure by restoration of normoxia should allow antioxidant defenses to be maintained or possibly even enhanced.

Frank et al (26) found that tolerance to oxygen exposure at 1.0 ATA could be greatly increased in rats by a "type" of intermittent exposure in which the rats were exposed to oxygen for 48 hours, returned to air for 12 to 24 hours, then reexposed to oxygen for 72 to 168 additional hours. Whereas continuous oxygen exposure for 72-168 hours was lethal for all control rats, the pre-exposed rats survived the additional exposure with only slight pulmonary edema. The increased oxygen tolerance was associated with statistically significant increments in pulmonary concentrations of superoxide dismutase, catalase, and glutathione peroxidase.

Harabin et al (27) studied the role of antioxidant enzymes in the increased oxygen tolerance afforded to guinea pigs and rats exposed intermittently to oxygen at 2.8 ATA in a cycle that alternated 10-minute oxygen periods with 2.5-minute intervals of air breathing (0.59 ATA PO₂). Intermittent exposure significantly increased convulsion and survival times in both species. Brain antioxidant enzyme activities were not significantly increased in either species. Lung superoxide dismutase activities were significantly increased during intermittent exposure in both species and were also increased in the rat during continuous exposure. In the guinea pig, activities of glutathione peroxidase in both lung and brain, and lung catalase activities were reduced further during continuous than during intermittent exposure. As indicated by the authors, these complex results did not fully explain the observed increments in oxygen tolerance. Only one pattern of intermittent exposure was studied at a single pressure.

Our results appear to indicate that the 60:15 sequence afforded greater protection of oxygen tolerance than the 30:30 sequence during the initial hours of intermittent exposure, but eventually became overwhelmed as the exposure continued. On the other hand, the 30:30 sequence was relatively ineffective initially, but then became sufficiently effective to stabilize or reverse earlier decrements in both visual and pulmonary function during the final hours of intermittent exposure. It is of interest that the changes in ERG b-wave amplitude appeared to show these effects more clearly than concurrent changes in FVC. This may reflect the fact that the ERG b-wave represents a composite response of two retinal cell types (bipolar and glial cells), while the changes in FVC are probably more complex and can be influenced by more variables.

One possible interpretation of our results can be based on the hypothesis that extension of oxygen tolerance by intermittent exposure depends not only upon cyclical periods of recovery from

oxygen poisoning, but also involves the concurrent augmentation of antioxidant defenses or some other means of oxygen tolerance enhancement. Previous animal studies have shown that antioxidant defenses can be enhanced by sufficiently prolonged exposure to toxic, sublethal levels of hyperoxia (28,29). It is possible that the 60:15 intermittent exposure pattern, by virtue of an inherently greater level of toxicity, initiated the enhancement of antioxidant defenses at an earlier time than the 30:30 pattern, but was unable to sustain the level of production required for continued protection. If the proposed hypothesis can be confirmed, it may be possible to increase the benefits of intermittent exposure by selecting appropriate patterns for different parts of a prolonged exposure, or by basing the choice of a single pattern on the expected duration of exposure.

Operational Relevance of Observed Results

Optimization of oxygen tolerance extension by intermittent hyperoxic exposure will provide prominent and permanent enhancement of Navy mission in diving operations, decompression methods, and hyperoxygenation therapy. The research results are relevant to both procedure and probability of success in all forms of Navy diving. Extension of CNS (visual) and pulmonary oxygen tolerance to increased oxygen pressures relates specifically and critically to both safety and operational effectiveness in undersea operations, as well as to improvement in therapy of gas lesion diseases. Although extension of oxygen tolerance by intermittent exposure has been studied only at rest to date, concurrent studies indicate that the adverse effects of exercise on oxygen tolerance may be avoided by preventing the hypercapnia and associated increments in brain blood flow and oxygen dose that occur during oxygen breathing at increased ambient pressures (30). Validation of this working hypothesis will provide a basis for extension of oxygen tolerance during exercise as well as at rest.

Our results show that both visual and pulmonary oxygen tolerance can be extended significantly at 2.0 ATA by systematic alternation of oxygen and normoxic exposure periods. They also show clearly for the first time in man or in animals that early toxic effects on the eye and lung can be stabilized or reversed at least partially during continued intermittent exposure with an appropriate combination of oxygen exposure and normoxic recovery periods. The extents to which such reversals will occur at other oxygen pressures and with other effects of oxygen toxicity remain to be determined. Elucidation of the mechanisms for such responses should provide information that can be widely exploited in the development of more effective means for extension of oxygen tolerance than those that are now available.

REFERENCES

1. Hendricks, P.L., D.A. Hall, W.L. Hunter, Jr., and P.J. Haley. Extension of pulmonary O₂ tolerance in man at 2 ATA by intermittent O₂ exposure. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 42:593-599, 1977.
2. Clark, J.M. Oxygen toxicity. In: Bennett, P.B., and D.H. Elliott, eds. The Physiology and Medicine of Diving, 4th. ed. London: Balliere Tindall. In press.
3. Lambertsen, C.J. Effects of hyperoxia on organs and their tissues. In: Robin, E.D., ed. *Extrapulmonary Manifestations of Respiratory Disease*. Vol. 8 of *Lung Biology in Health and Disease*, ed. by C. Lenfant. New York: Marcel Dekker. 1978. pp. 239-303.
4. U.S. Navy Diving Manual. NAVSEA 0994-LP-001-9020, REVISION 3. Washington, D.C.: US Government Printing Office. 1991.
5. Lambertsen, C.J., J.M. Clark, R. Gelfand, J.B. Pisarello, W.H. Cobbs, J.E. Bevilacqua, D.M. Schwartz, D.J. Montabana, C.S. Leach, P.C. Johnson, and D.E. Fletcher. Definition of tolerance to continuous hyperoxia in man. An abstract report of Predictive Studies V. In: Bove, A.A., A.J. Bachrach, and L.J. Greenbaum, eds. *Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology*. Bethesda: Undersea and Hyperbaric Medical Society. 1987. pp. 717-735.
6. Clark, J.M., R. Gelfand, N.D. Flores, C.J. Lambertsen, and J.B. Pisarello. Pulmonary tolerance in man to continuous oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA in Predictive Studies V. In: Bove, A.A., A.J. Bachrach, and L.J. Greenbaum, eds. *Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology*. Bethesda: Undersea and Hyperbaric Medical Society. 1987. pp. 737-749.
7. Gelfand, R., J.M. Clark, C.J. Lambertsen, and J.B. Pisarello. Effects on respiratory homeostasis of prolonged continuous hyperoxia at 1.5 to 3.0 ATA in man in Predictive Studies V. In: Bove, A.A., A.J. Bachrach, and L.J. Greenbaum, eds. *Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology*. Bethesda: Undersea and Hyperbaric Medical Society. 1987. pp. 751-761.

8. Pisarello, J.B., J.M. Clark, C.J. Lambertsen, and R. Gelfand. Human circulatory responses to prolonged hyperbaric hyperoxia in Predictive Studies V. In: Bove, A.A., A.J. Bachrach, and L.J. Greenbaum, eds. Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology. Bethesda: Undersea and Hyperbaric Medical Society. 1987. pp. 763-772.
9. Lambertsen, C.J. Respiratory and circulatory actions of high oxygen pressure. In: Goff, L.G., ed. Proceedings of the Underwater Physiology Symposium. Washington, D.C.: National Academy of Sciences (National Research Council Publ. 377). 1955. pp. 25-38.
10. Hall, D.A. The influence of the systematic fluctuation of PO_2 upon the nature and rate of the development of oxygen toxicity in guinea pigs. Philadelphia: University of Pennsylvania. 1967. (Master of Science Thesis).
11. Fletcher, D.E., C.J. Lambertsen, R. Gelfand, J.M. Clark, and R.E. Peterson. Perceptual, memory, cognitive, and psychomotor functions. In: Lambertsen, C.J., R. Gelfand, and J.M. Clark, eds. Predictive Studies IV. Work Capability and Physiological Effects in He- O_2 Excursions to Pressures of 400-800-1200 and 1600 Feet of Sea Water. Institute for Environmental Medicine Report 78-1. Philadelphia: University of Pennsylvania, 1978. pp. E10-1 to E10-58.
12. Clark, J.M., C.J. Lambertsen, D.J. Montabana, R. Gelfand, and W.H. Cobbs. Comparison of visual function effects in man during continuous oxygen exposures at 3.0 and 2.0 ATA for 3.4 and 9.0 hours (in Predictive Studies V). Undersea Biomedical Research 15(Supp.):32, 1988.
13. Clark, J.M., and C.J. Lambertsen. Rate of development of pulmonary O_2 toxicity in man during O_2 breathing at 2.0 atm abs. J. Appl. Physiol. 30:739-752, 1971.
14. Clark, J.M. Pulmonary limits of oxygen tolerance in man. Experimental Lung Research 14:897-910, 1988.
15. Fisher, A.B., R.W. Hyde, R.J.M. Puy, J.M. Clark, and C.J. Lambertsen. Effect of oxygen at 2 atmospheres on the pulmonary mechanics of normal man. J. Appl. Physiol. 24:529-536, 1968.
16. Clark, J.M., R.M. Jackson, C.J. Lambertsen, R. Gelfand, W.D.B. Hiller, and M. Unger. Pulmonary function in men after oxygen breathing at 3.0 ATA for 3.5 h. J. Appl. Physiol. 71: 878-885, 1991.

17. Puy, R.J.M., R.W. Hyde, A.B. Fisher, J.M. Clark, J. Dickson, and C.J. Lambertsen. Alterations in the pulmonary capillary bed during early O₂ toxicity in man. *J. Appl. Physiol.* 24:537-543, 1968.
18. Bulow, K. Respiration and wakefulness in man. *Acta. Physiol. Scand.* 59(Supp. 209):1-110, 1963.
19. Clark, J.M., R.D. Sinclair, and B. E. Welch. Rate of acclimatization to chronic hypercapnia in man. In: Lambertsen, C.J., ed. *Underwater Physiology IV*. New York: Academic Press. 1971. pp. 399-408.
20. Dickens, F. The toxic effects of oxygen on brain metabolism and on tissue enzymes. *Biochem. J.* 40:145-186, 1946.
21. Stadie, W.C., B.C. Riggs, and N. Haugaard. Oxygen poisoning. III. The effect of high oxygen pressures upon the metabolism of brain. *J. Biol. Chem.* 160:191-208, 1945.
22. Stadie, W.C., B.C. Riggs, and N. Haugaard. Oxygen poisoning. IV. The effect of high oxygen pressures upon the metabolism of liver, kidney, lung and muscle tissue. *J. Biol. Chem.* 160:209-216, 1945.
23. Lambertsen, C.J. Extension of oxygen tolerance in man: philosophy and significance. *Experimental Lung Research* 14:1035-1058, 1988.
24. Jamieson, D. Oxygen toxicity and reactive oxygen metabolites in mammals. *Free Radical Biology and Medicine* 7:87-108, 1989.
25. Fisher, A.B., D.J.P. Bassett, and H.J. Forman. Oxygen toxicity of the lung: biochemical aspects. In: Fishman, A.P. and E.M. Renkin, eds. *Pulmonary Edema*. Bethesda: American Physiological Society. 1979. pp. 207-216.
26. Frank, L., J. Iqbal, M. Hass, and D. Massaro. New "rest period" protocol for inducing tolerance to high O₂ exposure in adult rats. *Am. J. Physiol.* 257 (Lung Cell. Mol. Physiol. 1):L226-L231, 1989.
27. Harabin, A.L., J.C. Braisted, and E.T. Flynn. Response of antioxidant enzymes to intermittent and continuous hyperbaric oxygen. *J. Appl. Physiol.* 69:328-335, 1990.
28. Crapo, J.D., and D.F. Tierney. Superoxide dismutase and pulmonary oxygen toxicity. *Am. J. Physiol.* 226:1401-1407, 1974.

29. Crapo, J.D., B.E. Barry, H.A. Foscue, and J.S. Shelburne. Structural and biochemical changes in rat lungs occurring during oxygen exposures to lethal and adaptive doses of oxygen. Am. Rev. Respir. Dis. 122:123-143, 1978.

30. Clark, J.M. and C.J. Lambertsen. Extension of central nervous and visual system oxygen tolerance in physical work. Combined Final Report for Contract Nos. N00014-88-K-0270 and N00014-88-K-0318. Bethesda: Naval Medical Research and Development Command. 1990.

PROGRAM PUBLICATIONS

1. Lambertsen, C.J., J.M. Clark, R. Gelfand, J.B. Pisarello, W.H. Cobbs, J.E. Bevilacqua, D.M. Schwartz, D.J. Montabana, C.S. Leach, P.C. Johnson, and D.E. Fletcher. Definition of tolerance to continuous hyperoxia in man. An abstract report of Predictive Studies V. In: Bove, A.A., A.J. Bachrach, and L.J. Greenbaum, eds. Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology. Bethesda: Undersea and Hyperbaric Medical Society. 1987. pp. 717-735.
2. Clark, J.M., R. Gelfand, N.D. Flores, C.J. Lambertsen, and J.B. Pisarello. Pulmonary tolerance in man to continuous oxygen exposure at 3.0, 2.5, 2.0, and 1.5 ATA in Predictive Studies V. In: Bove, A.A., A.J. Bachrach, and L.J. Greenbaum, eds. Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology. Bethesda: Undersea and Hyperbaric Medical Society. 1987. pp. 737-749.
3. Gelfand, R., J.M. Clark, C.J. Lambertsen, and J.B. Pisarello. Effects on respiratory homeostasis of prolonged continuous hyperoxia at 1.5 to 3.0 ATA in man in Predictive Studies V. In: Bove, A.A., A.J. Bachrach, and L.J. Greenbaum, eds. Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology. Bethesda: Undersea and Hyperbaric Medical Society. 1987. pp. 751-761.
4. Pisarello, J.B., J.M. Clark, C.J. Lambertsen, and R. Gelfand. Human circulatory responses to prolonged hyperbaric hyperoxia in Predictive Studies V. In: Bove, A.A., A.J. Bachrach, and L.J. Greenbaum, eds. Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology. Bethesda: Undersea and Hyperbaric Medical Society. 1987. pp. 763-772.
5. Gelfand, R., J.M. Clark, C.J. Lambertsen, and J. Pisarello. Ventilatory response to hypoxia following prolonged hyperoxia at 1.5 ATA in man. Fed. Proc. 46(3):827, 1987.
6. Clark, J.M., R. Gelfand, N.D. Flores, J. Pisarello, and C.J. Lambertsen. Pulmonary function alterations and symptoms in man during and after O₂ exposure at 2.5 ATA for 5-6 hours. Amer. Rev. Resp. Dis. 135 (4):A265, 1987.
7. Gelfand, R., J.M. Clark, and C.J. Lambertsen. Effects on body temperature of continuous hyperoxia at 1.5, 2.0, 2.5, and 3.0 ATA in man (in Predictive Studies V). Undersea Biomed. Res. 14(Supp.):28, 1987.

8. Clark, J.M., ed. Symposium on Extension of Oxygen Tolerance. Experimental Lung Research 14(Supp.):865-1058, 1988.
9. Clark, J.M. Pulmonary limits of oxygen tolerance in man. Experimental Lung Research 14:897-910, 1988.
10. Lambertsen, C.J. Extension of oxygen tolerance in man: Philosophy and significance. Experimental Lung Research 14:1035-1058, 1988.
11. Lambertsen, C.J. Physiologic factors in human organ oxygen tolerance extension. In: On Diving and Hyperbaric Medicine and Diving Medical Advisory Committee Workshop. European Undersea Biomedical Society. Aberdeen, Scotland. Sept., 1988.
12. Clark, J.M., C.J. Lambertsen, D.J. Montabana, R. Gelfand, and W.H. Cobbs. Comparison of visual function effects in man during continuous oxygen exposures at 3.0 and 2.0 ATA for 3.4 and 9.0 hours (in Predictive Studies V). Undersea Biomedical Research 15(Supp.):32, 1988.
13. Gelfand, R., J.M. Clark, C.J. Lambertsen, and J.B. Pisarello. Ventilatory response to hypoxia following prolonged hyperoxia at 2.5 ATA in man (in Predictive Studies V). Undersea Biomedical Research 15(Supp.):34-35, 1988.
14. Gelfand, R., J.M. Clark, C.J. Lambertsen, and J.B. Pisarello. Ventilatory response to CO₂ following prolonged hyperoxia at 1.5 ATA and 2.5 ATA in man. FASEB J. 2(5):A1508, 1988.
15. Gelfand, R., J.M. Clark, and C.J. Lambertsen. Respiratory control timing characteristics during prolonged hyperoxia at 1.5, 2.0, 2.5, and 3.0 ATA (Predictive Studies V). Undersea Biomedical Research 16(Supp.):93-94, 1989.
16. Clark, J.M. and C.J. Lambertsen. Principles of oxygen tolerance extension defined in the rat by intermittent oxygen exposure at 2.0 and 4.0 ATA. Undersea Biomedical Research 16(Supp.):99, 1989.
17. Clark, J.M. Oxygen tolerance in nitrox diving. In: Hamilton, R.W., D.J. Crosson, and A.W. Hulbert, eds. Workshop on Enriched Air Nitrox Diving. National Undersea Research Program Research Report 89-1, National Oceanic and Atmospheric Administration, 1989. pp. 51-74.
18. Thom, S.R. and J.M. Clark. The toxicity of oxygen, carbon monoxide, and carbon dioxide. In: Bove, A.A. and J.C. Davis, eds. Diving Medicine, 2nd ed. Philadelphia: W.B. Saunders. 1989. pp. 82-94.

19. Clark, J.M., R. Gelfand, and C.J. Lambertsen. Unexpected magnitude and rate of decline in human pulmonary mechanical function during O₂ exposure at 2.5 ATA for 5-6 hours. Aerospace Medical Association 60th Annual Scientific Meeting, 1989. p. A45.
20. Lambertsen, C.J., R. Gelfand, and J.M. Clark. Symptomatic and physiologic expressions of CNS oxygen poisoning in man. Aerospace Medical Association 60th Annual Scientific Meeting, 1989. p. A45.
21. Clark, J.M., R. Gelfand, W.C. Stevens, and C.J. Lambertsen. Extension of pulmonary oxygen tolerance in man at 2.0 ATA by intermittent exposure on a 60:15 oxygen:normoxic pattern in Predictive Studies VI. Undersea Biomed. Res. 17(Supp.):25, 1990.
22. Gelfand, R., J.M. Clark, and C.J. Lambertsen. Ventilatory response to hypoxia is preserved following prolonged hyperbaric hyperoxia at 1.5, 2.0, and 2.5 ATA in man (Predictive Studies V). Undersea Biomed. Res. 17(Supp.):163, 1990.
23. Stevens, W.C., J.M. Clark, R. Gelfand, and C.J. Lambertsen. Interacting effects of 2 ATA inspired PO₂ and exercise on pulmonary ventilation and arterial PCO₂. Undersea Biomed. Res. 17(Supp.):164-165, 1990.
24. Stevens, W.C., J.M. Clark, R. Gelfand, and C.J. Lambertsen. The effect of hyperbaric oxygen on selected cardiovascular and thermoregulatory parameters during exercise. Med. Sci. Sports Exerc. 22(Supp.):S91, 1990.
25. Clark, J.M. Therapeutic and toxic effects of hyperbaric oxygenation. In: Crystal, R.G. and J.B. West, eds. The Lung. Scientific Foundations. New York: Raven Press. 1991. pp. 2123-2131.
26. Clark, J.M., R. Gelfand, W.C. Stevens, and C.J. Lambertsen. Comparison of human visual and pulmonary responses to continuous and intermittent oxygen exposure at 2.0 ATA in Predictive Studies V and VI. Undersea Biomed. Res. 18(Supp.):86, 1991.
27. Gelfand, R., J.M. Clark, and C.J. Lambertsen. Ventilatory response to carbon dioxide is not diminished after human exposure to prolonged hyperbaric hyperoxia at 1.5, 2.0, and 2.5 ATA (Predictive Studies V). Undersea Biomed. Res. 18(Supp.):87, 1991.
28. Stevens, W.C., J.M. Clark, A.M. Paolone, R. Gelfand, and C.J. Lambertsen. Interacting effects of 2 ATA inspired PO₂ and exercise on cardiopulmonary parameters. Undersea Biomed. Res. 18(Supp.):89-90, 1991.

29. Clark, J.M., R.M. Jackson, C.J. Lambertsen, R. Gelfand, W.D.B. Hiller, and M. Unger. Pulmonary function in men after oxygen breathing at 3.0 ATA for 3.5 h. J. Appl. Physiol. 71: 878-885, 1991.
30. Clark, J.M. Oxygen toxicity. In: Bennett, P.B., and D.H. Elliott, eds. The Physiology and Medicine of Diving, 4th. ed. London: Balliere Tindall. In press.
31. Stevens, W.C., R. Gelfand, J.M. Clark, and C.J. Lambertsen. Core temperature in man during intermittent hyperoxia in Predictive Studies VI. Undersea Biomed. Res. 19(Supp.): 1992.
32. Clark, J.M., R. Gelfand, W.C. Stevens, and C.J. Lambertsen. Unexpected pattern of pulmonary and visual O₂ tolerance extension in man during intermittent hyperoxia at 2.0 ATA in Predictive Studies VI. Undersea Biomed. Res. 19(Supp.): 1992.
33. Gelfand, R., J.M. Clark, W.C. Stevens, and C.J. Lambertsen. Partial reversal of respiratory control timing effect of O₂ toxicity in man during intermittent hyperoxia at 2.0 ATA in Predictive Studies VI. Undersea Biomed. Res. 19(Supp.): 1992.

FINAL REPORT APPENDIX
EXTENSION OF OXYGEN TOLERANCE IN MAN
(PREDICTIVE STUDIES VI)
Contract No. N00014-88-K-0169
FIGURES AND TABLES

C. J. Lambertsen, M.D., Principal Investigator
J. M. Clark, M.D., Ph.D., Co-Principal Investigator

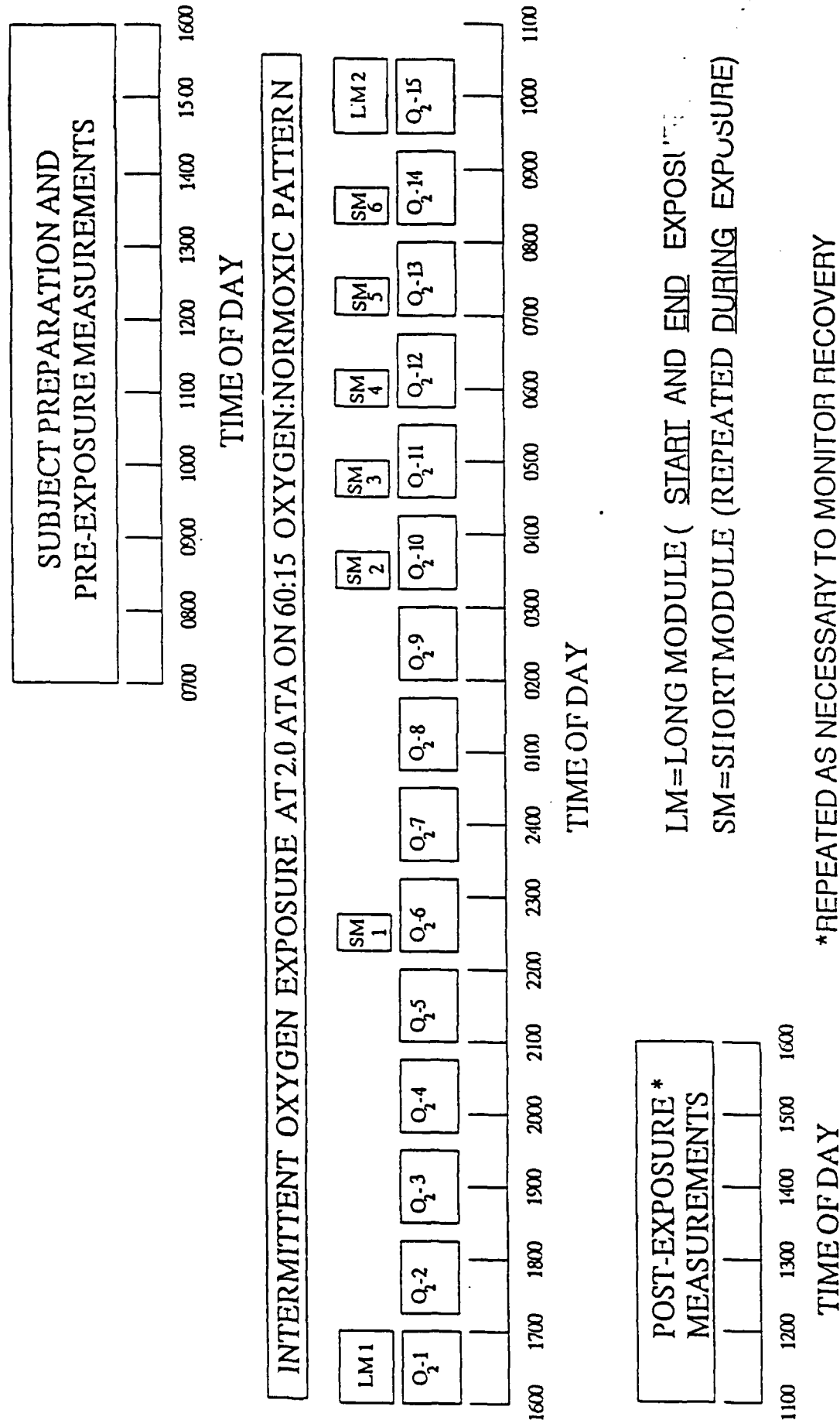
Institute For Environmental Medicine
University of Pennsylvania Medical Center
Philadelphia, PA 19104-6068

31 December 1991

APPENDIX

PREDICTIVE STUDIES VI EXPERIMENT PROTOCOL

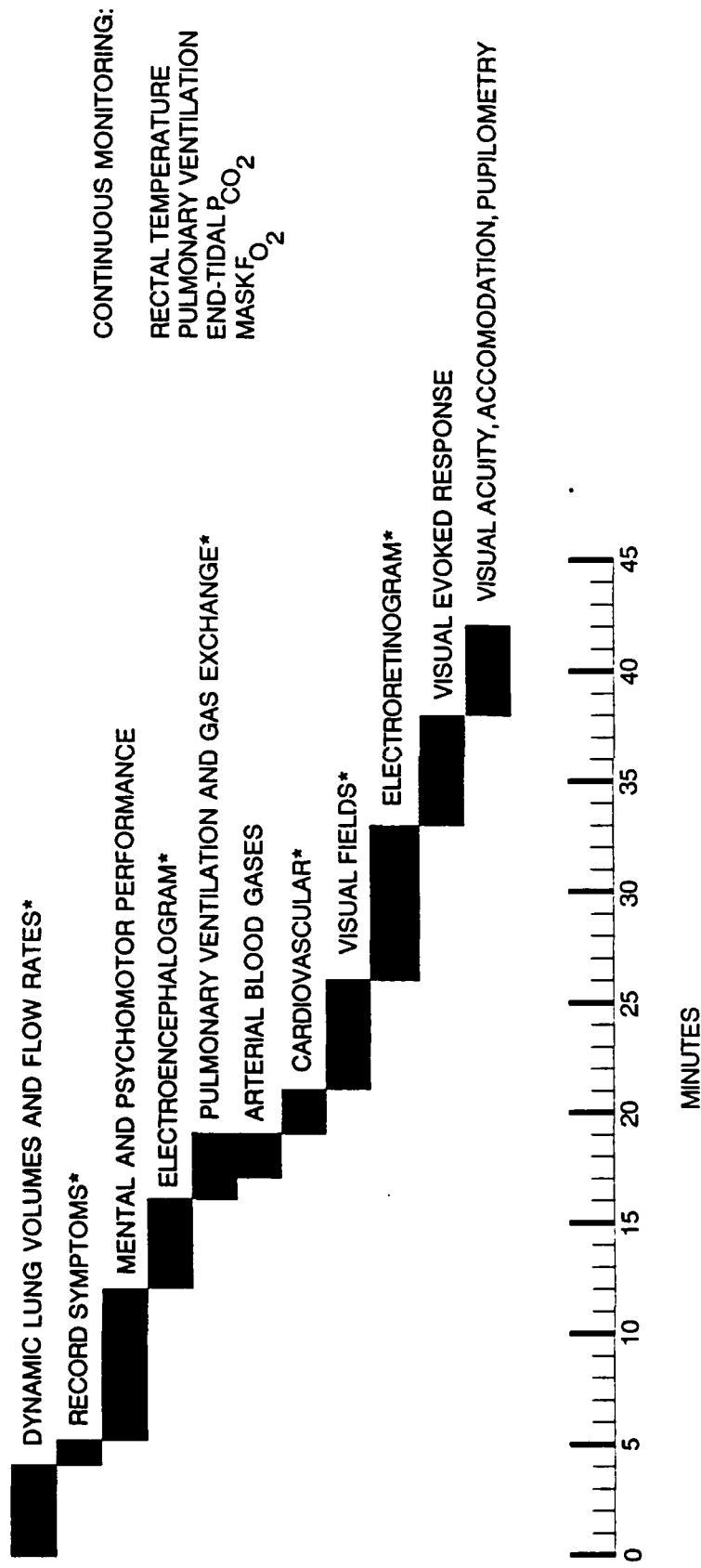
FOR 60:15 OXYGEN:NORMOXIC PATTERN OF ALTERNATION



Appendix Figure 2

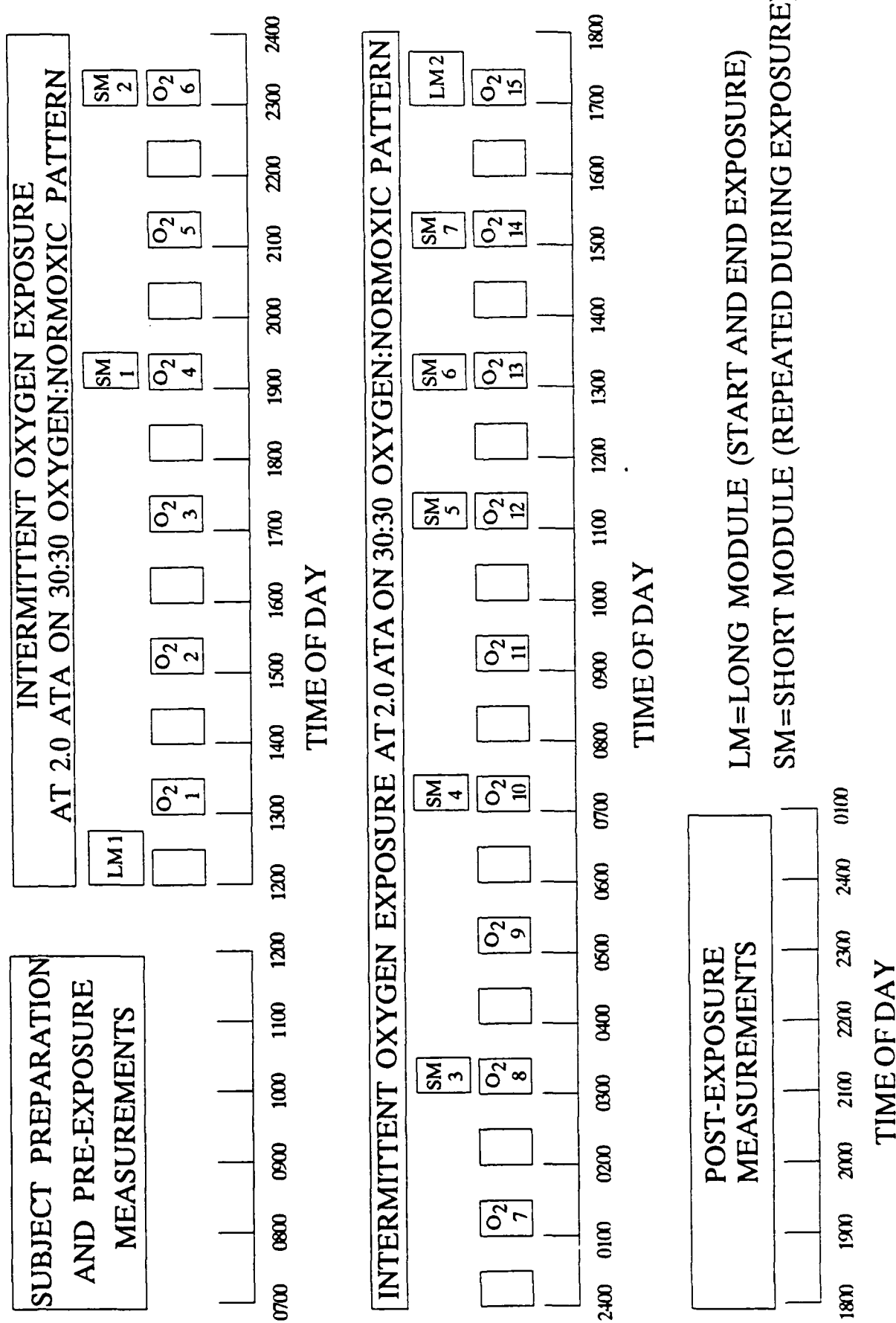
PREDICTIVE STUDIES VI MEASUREMENT MODULE INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA 60:15 OXYGEN:NORMOXIC PATTERN

LONG MODULE MEASUREMENTS **
 (*ALSO MEASURED IN SHORT MODULE)



** LONG MODULE (START AND END EXPOSURE)
 SHORT MODULE (REPEATED DURING EXPOSURE)

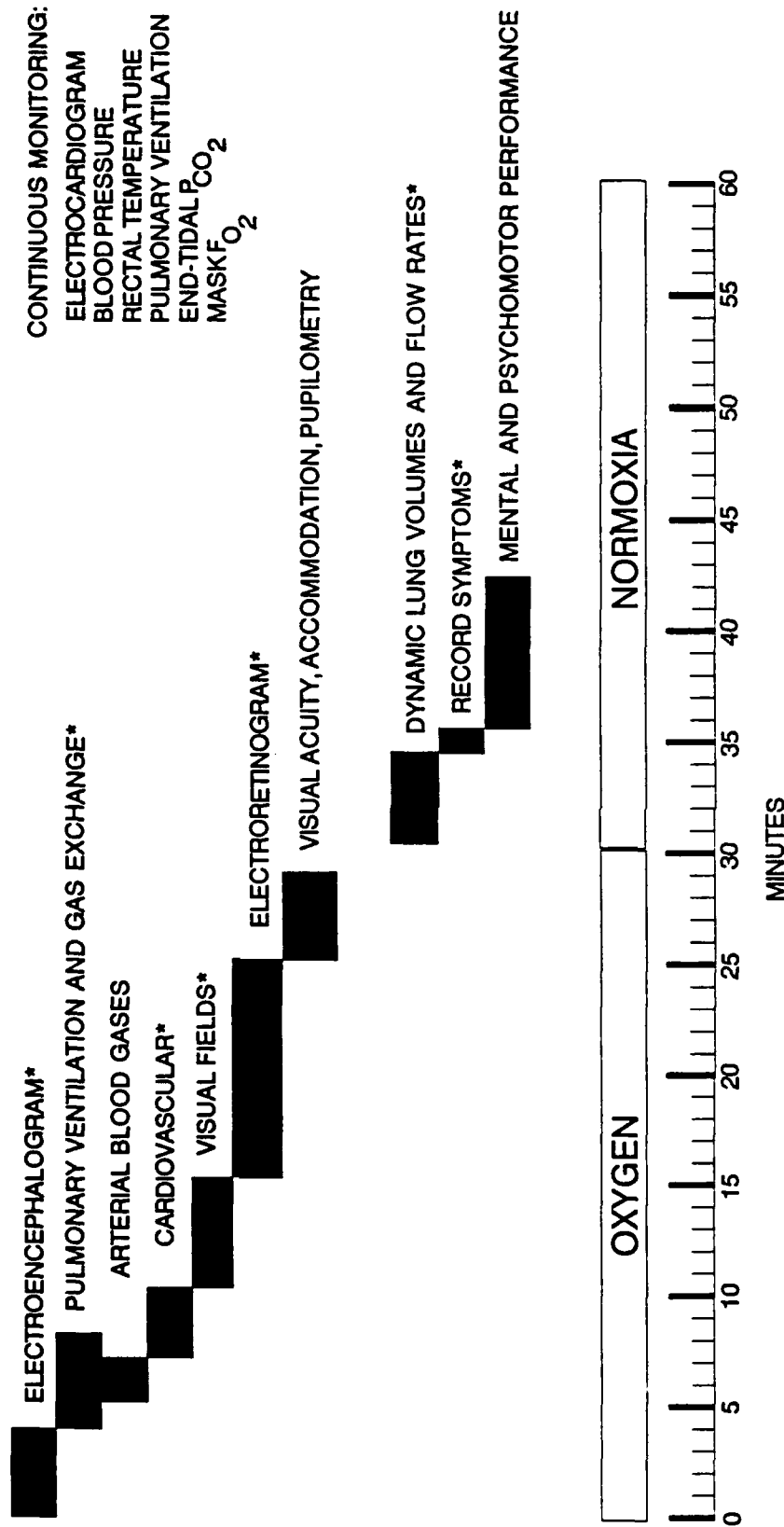
PREDICTIVE STUDIES VI EXPERIMENT PROTOCOL FOR 30:30 OXYGEN:NORMOXIC PATTERN OF ALTERNATION



Appendix Figure 4

PREDICTIVE STUDIES VI MEASUREMENT MODULE INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA 30:30 OXYGEN:NORMOXIC PATTERN

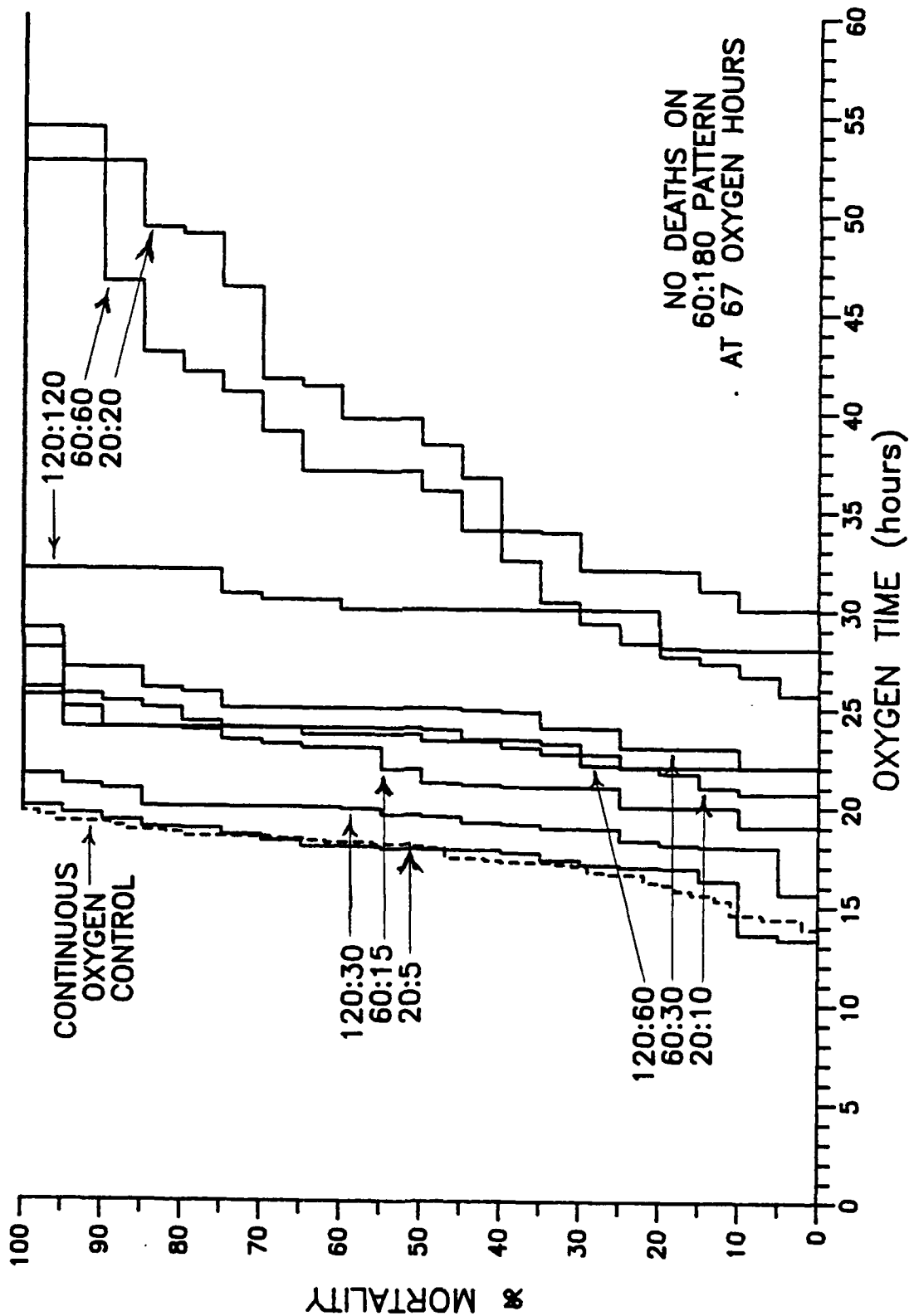
LONG MODULE MEASUREMENTS DONE AT START AND END OF EXPOSURE



* DENOTES SHORT MODULE MEASUREMENTS REPEATED DURING EXPOSURE

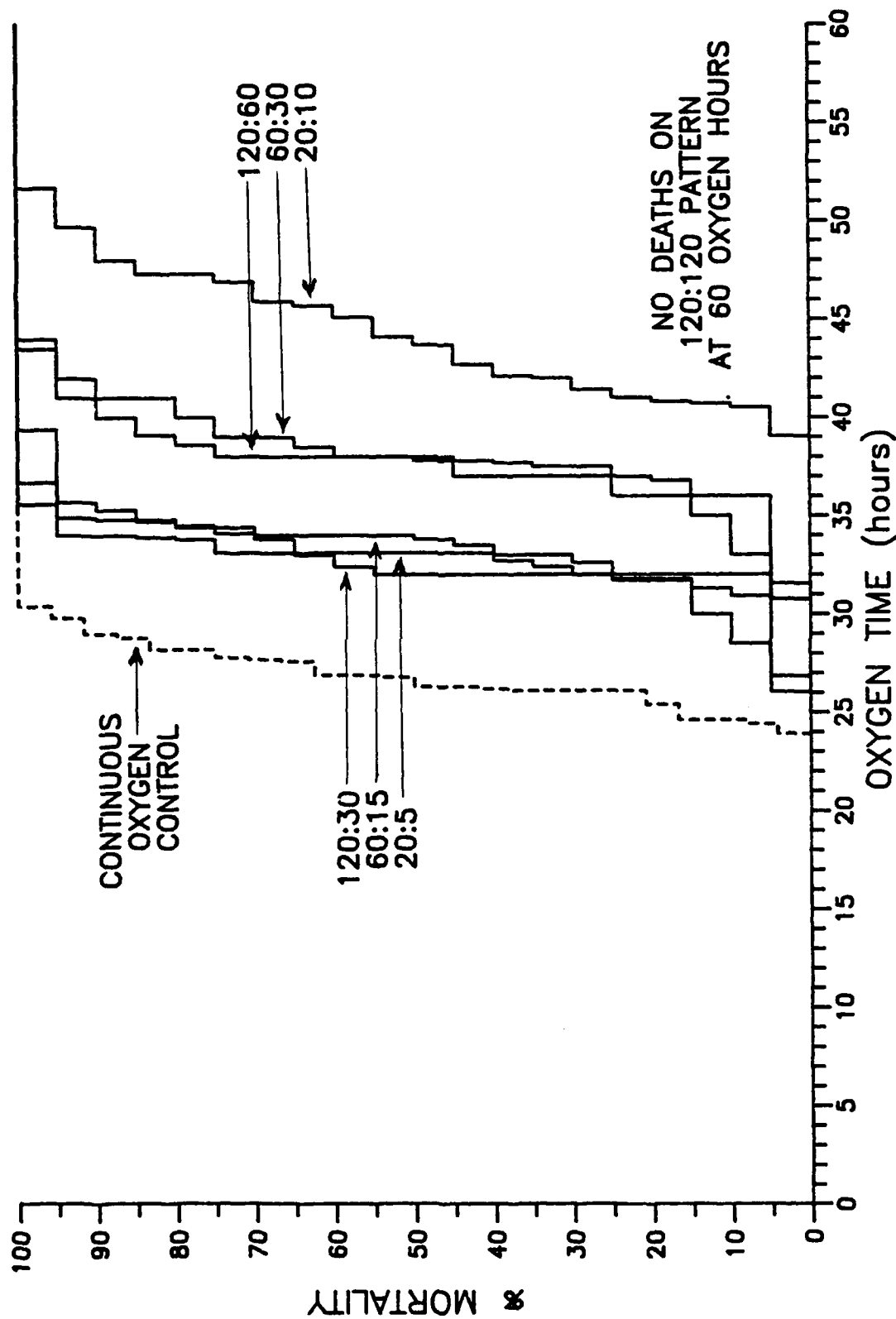
Appendix Figure 6

SURVIVAL TIME RESPONSES TO INTERMITTENT EXPOSURE PATTERNS AT AN OXYGEN PRESSURE OF 2.0 ATA IN RATS

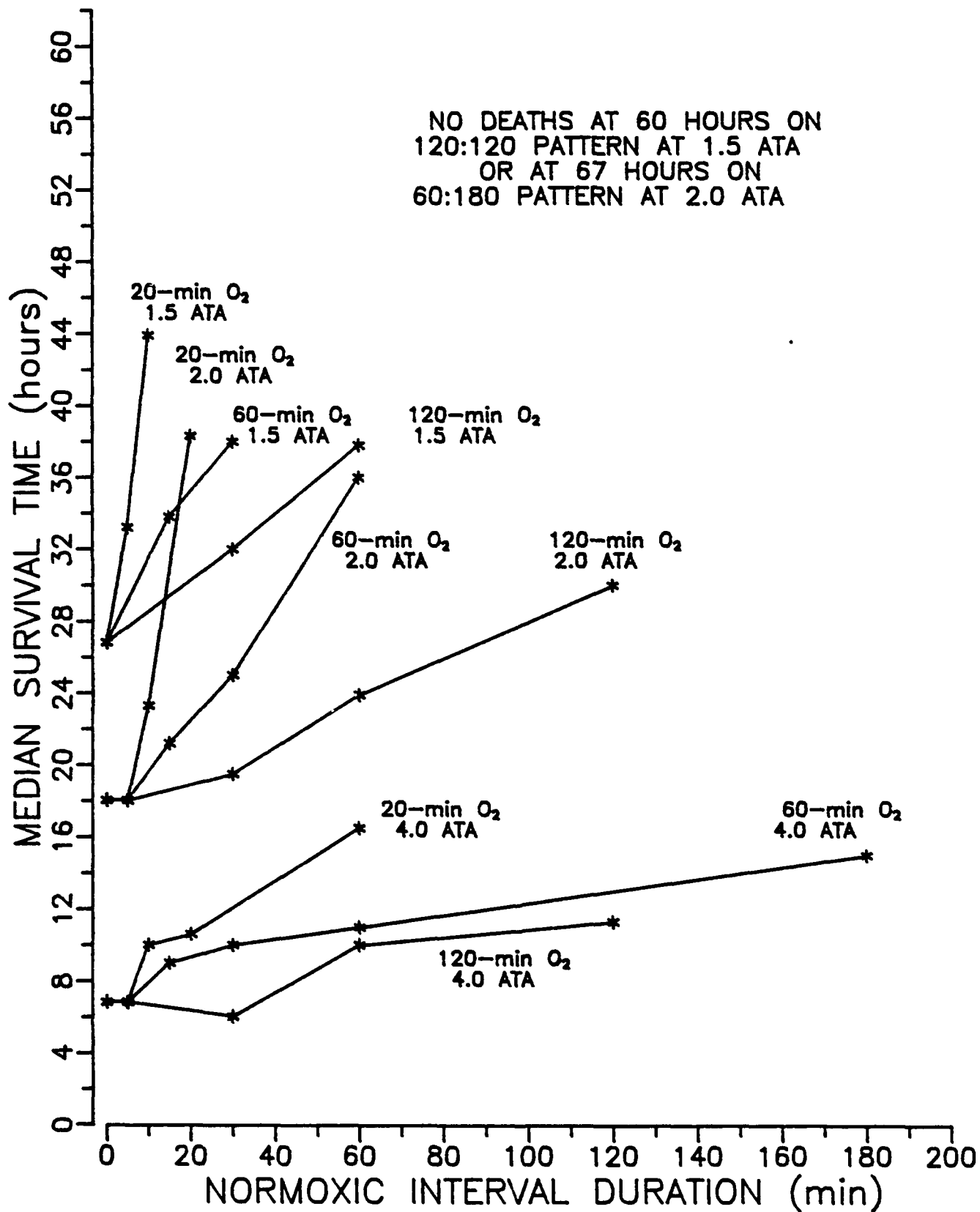


Appendix Figure 7

SURVIVAL TIME RESPONSES TO INTERMITTENT EXPOSURE PATTERNS AT AN OXYGEN PRESSURE OF 1.5 ATA IN RATS

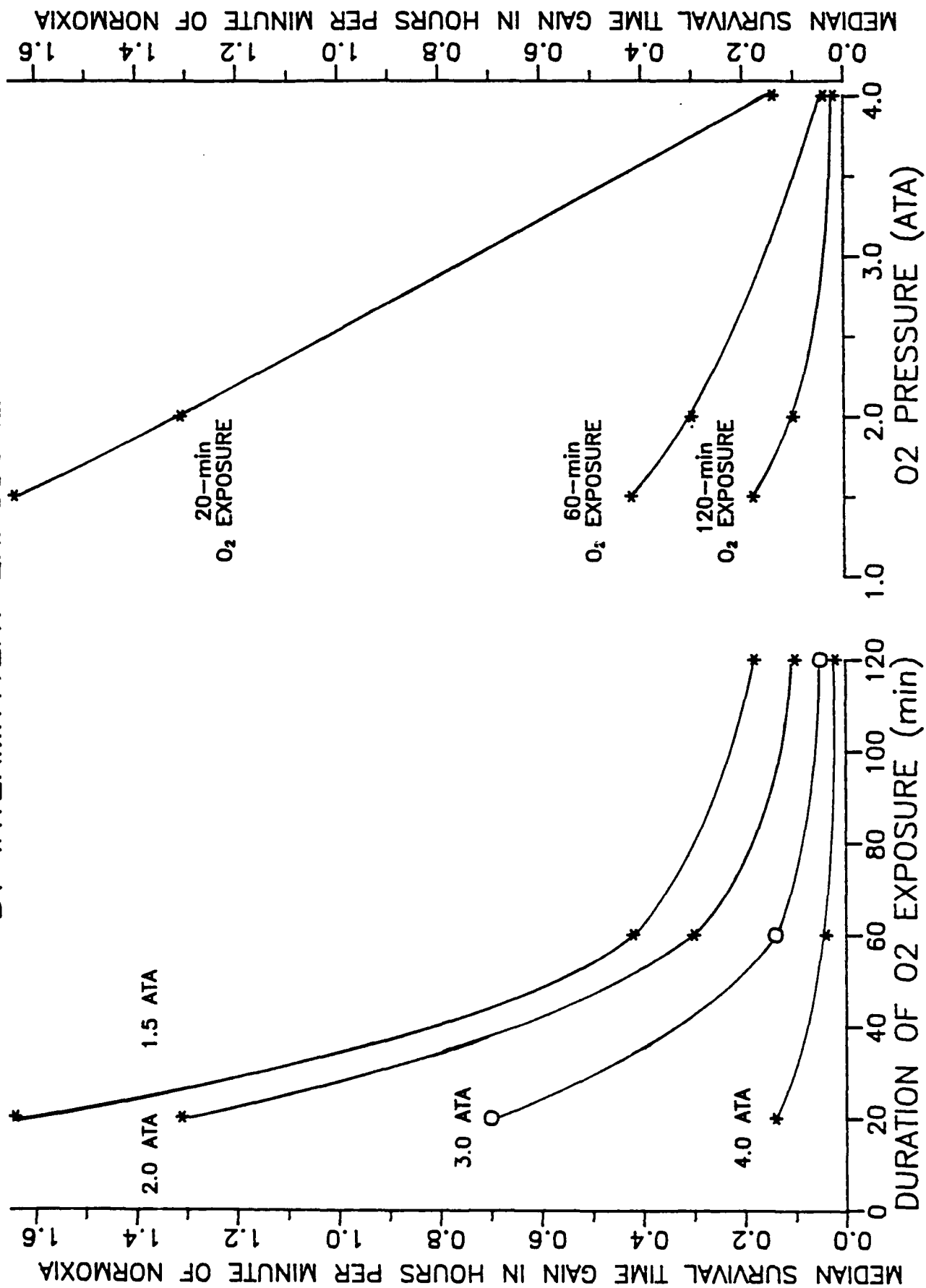


EXTENSION OF SURVIVAL TIME IN RATS BY INTERMITTENT OXYGEN EXPOSURE



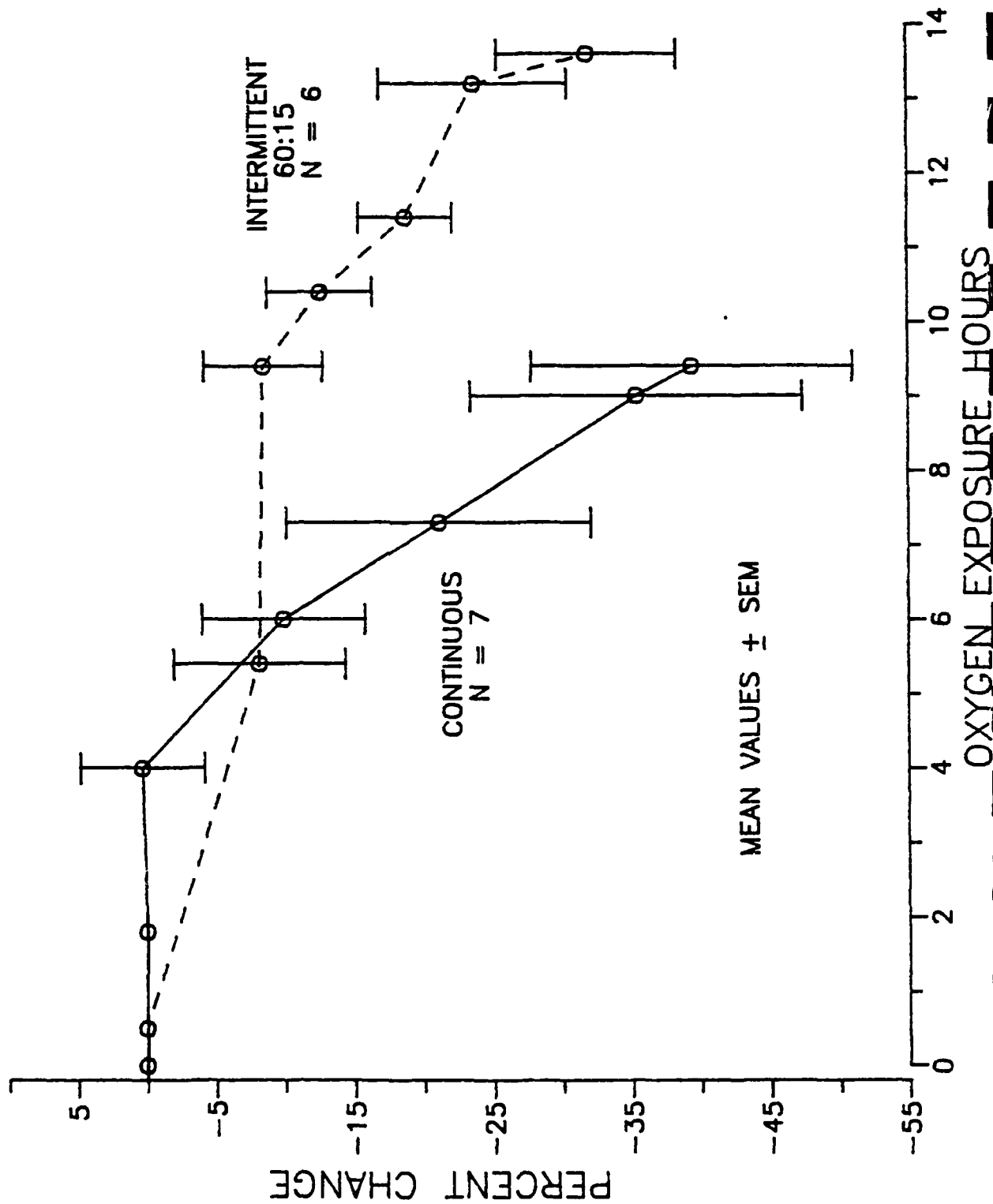
Appendix Figure 9

PREDICTION OF OXYGEN TOLERANCE EXTENSION BY INTERMITTENT EXPOSURE



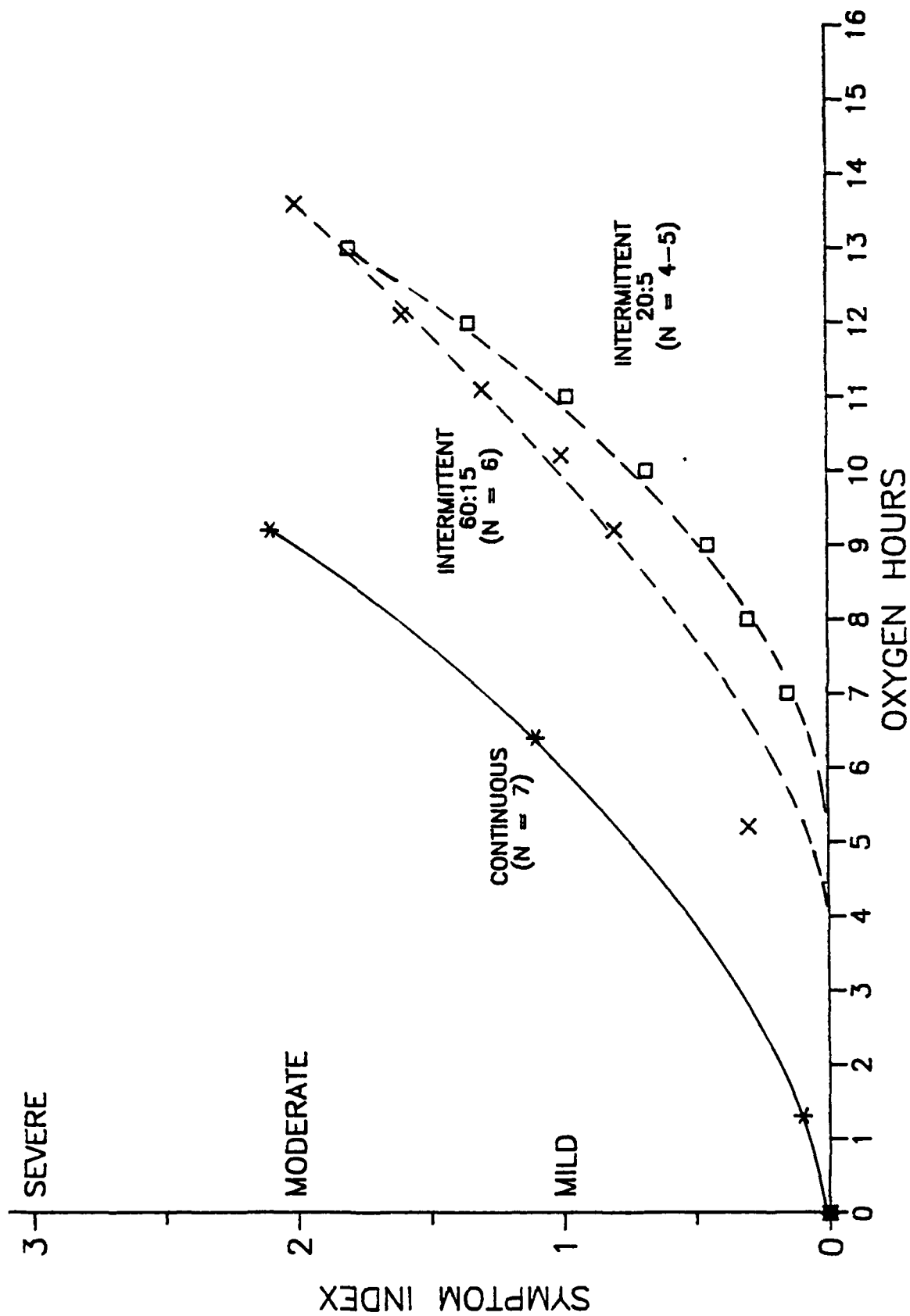
Appendix Figure 10

CHANGES IN ERG DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA



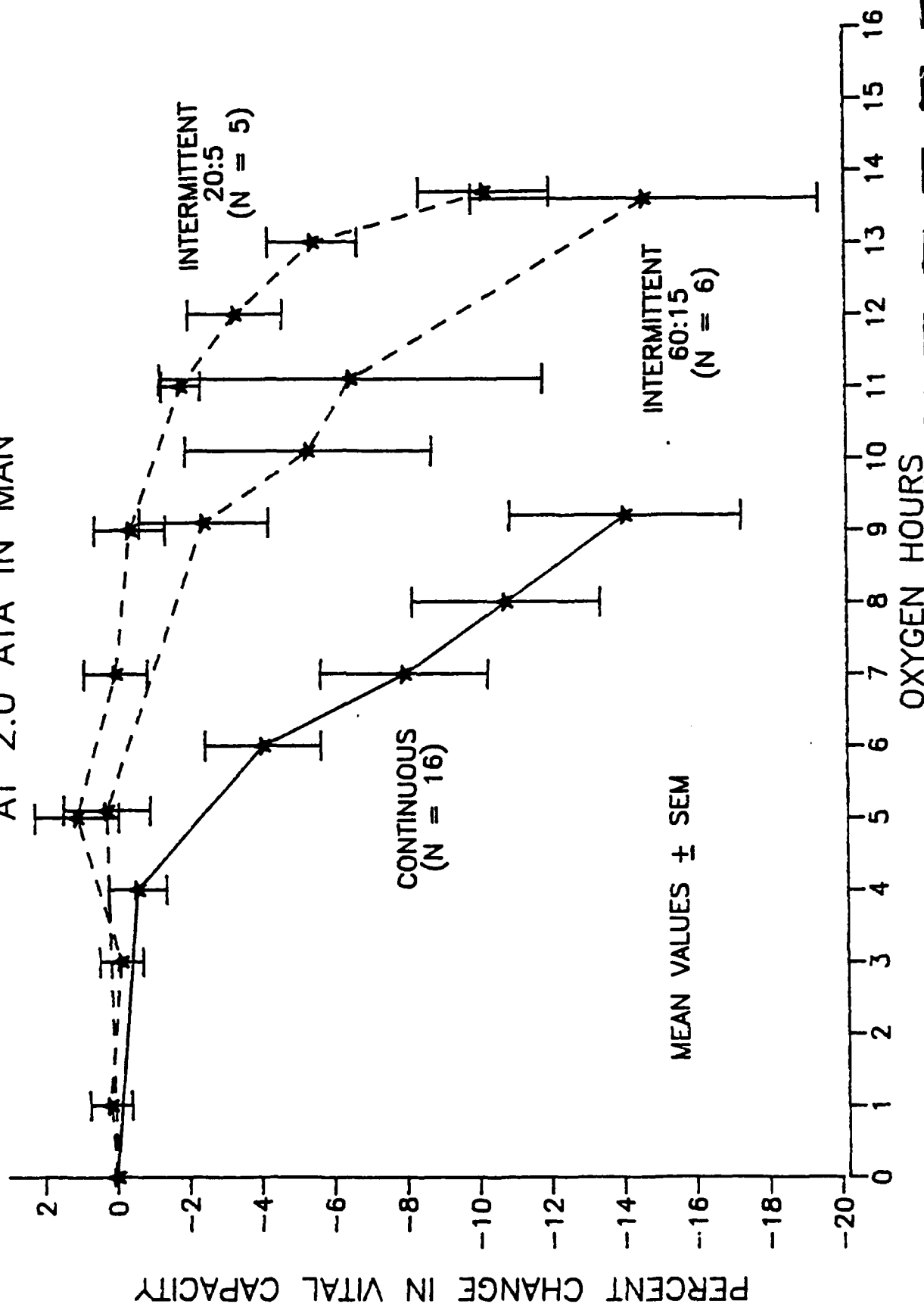
Appendix Figure 11

PULMONARY SYMPTOMS DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA IN MAN



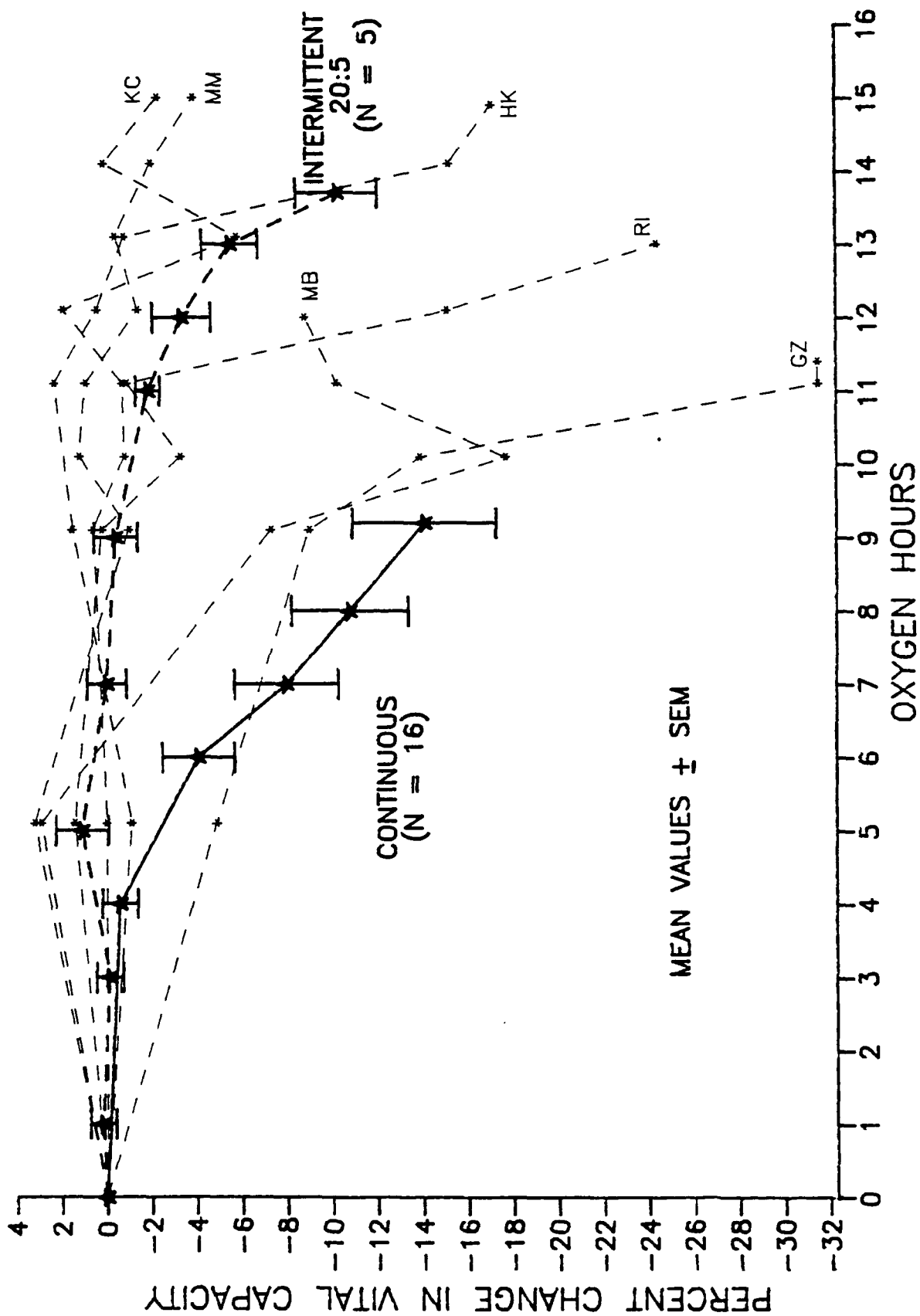
Appendix Figure 12

CHANGE IN VITAL CAPACITY DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA IN MAN



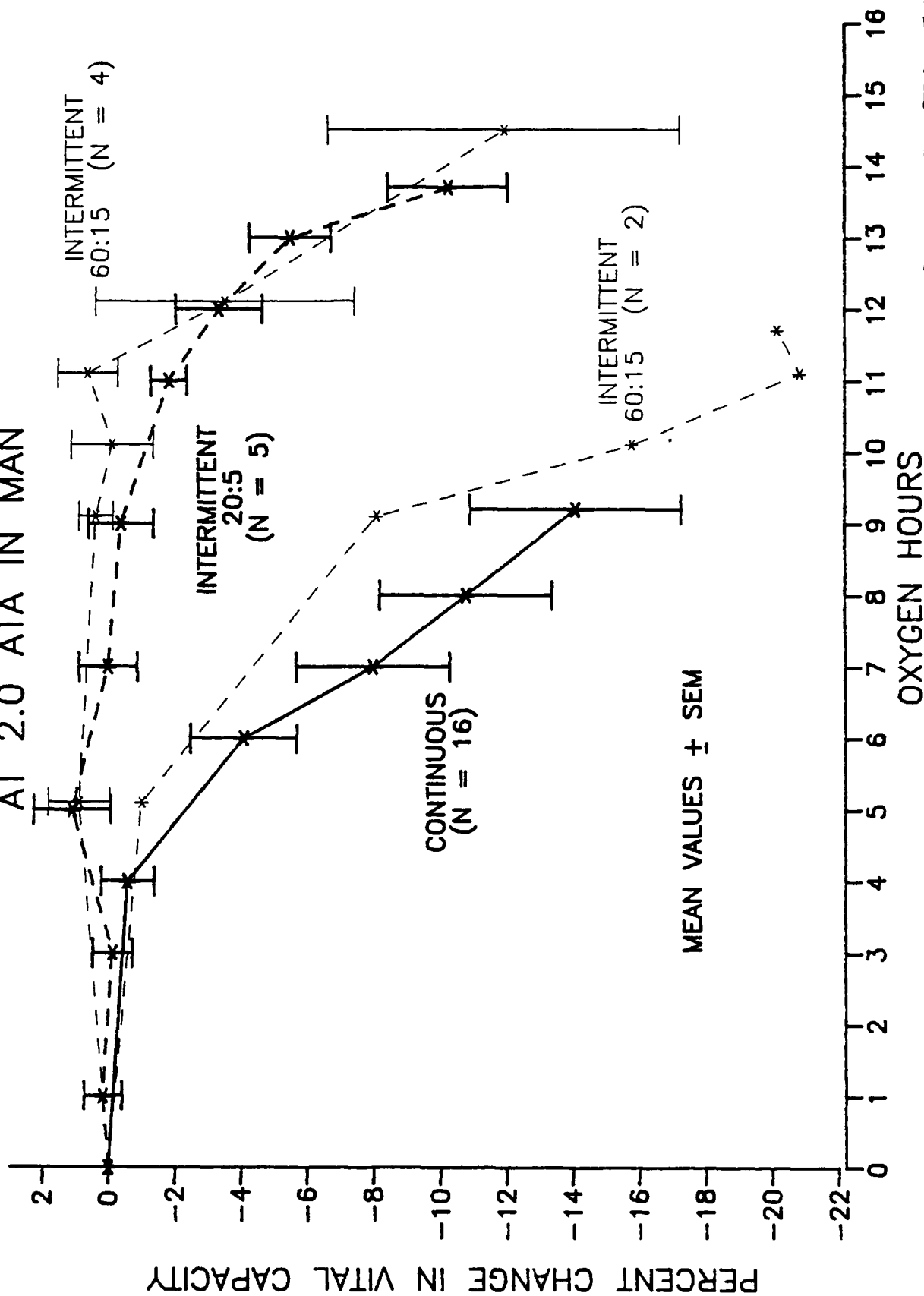
Appendix Figure 13

CHANGE IN VITAL CAPACITY DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA IN MAN



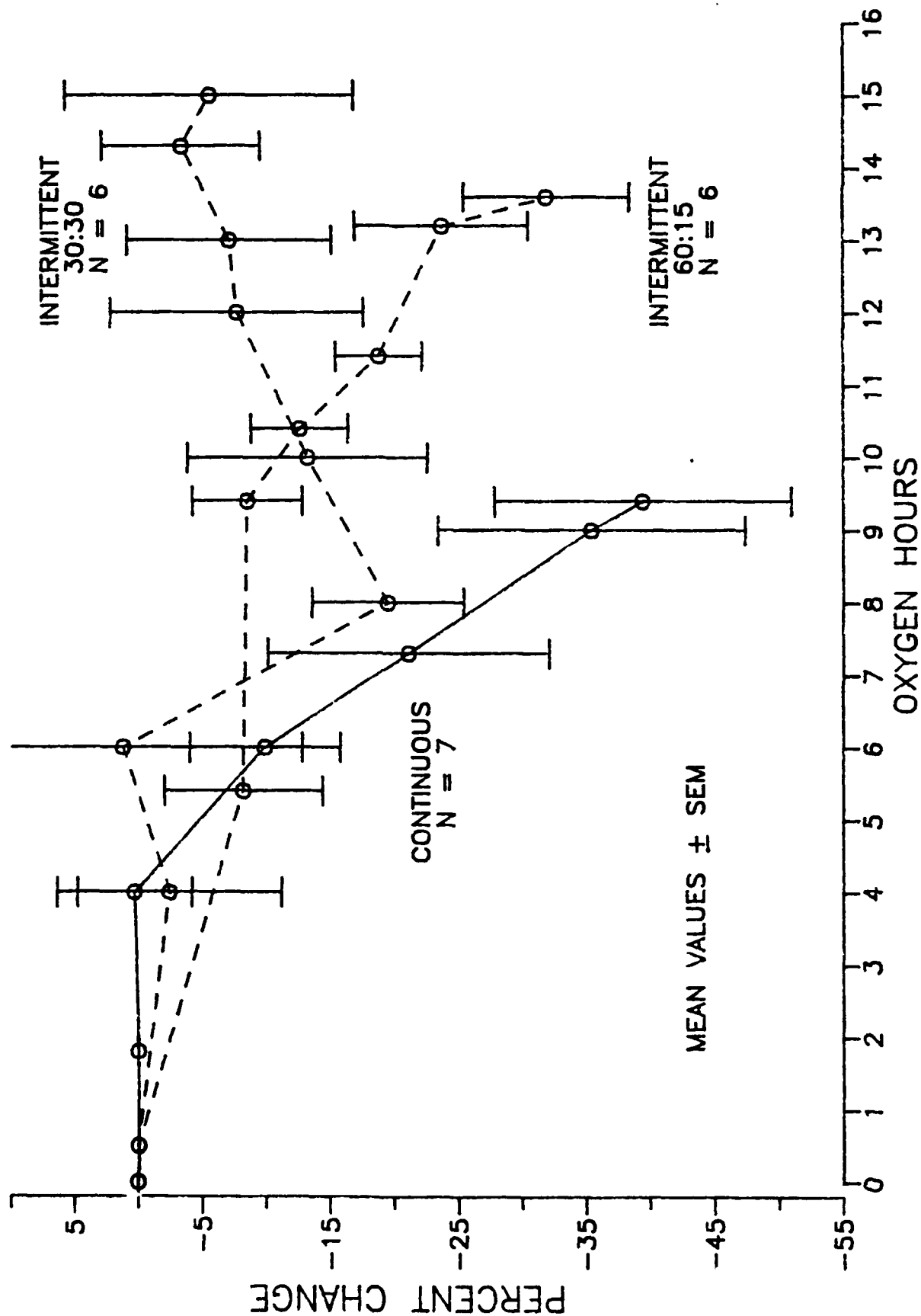
Appendix Figure 14

CHANGE IN VITAL CAPACITY DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA IN MAN



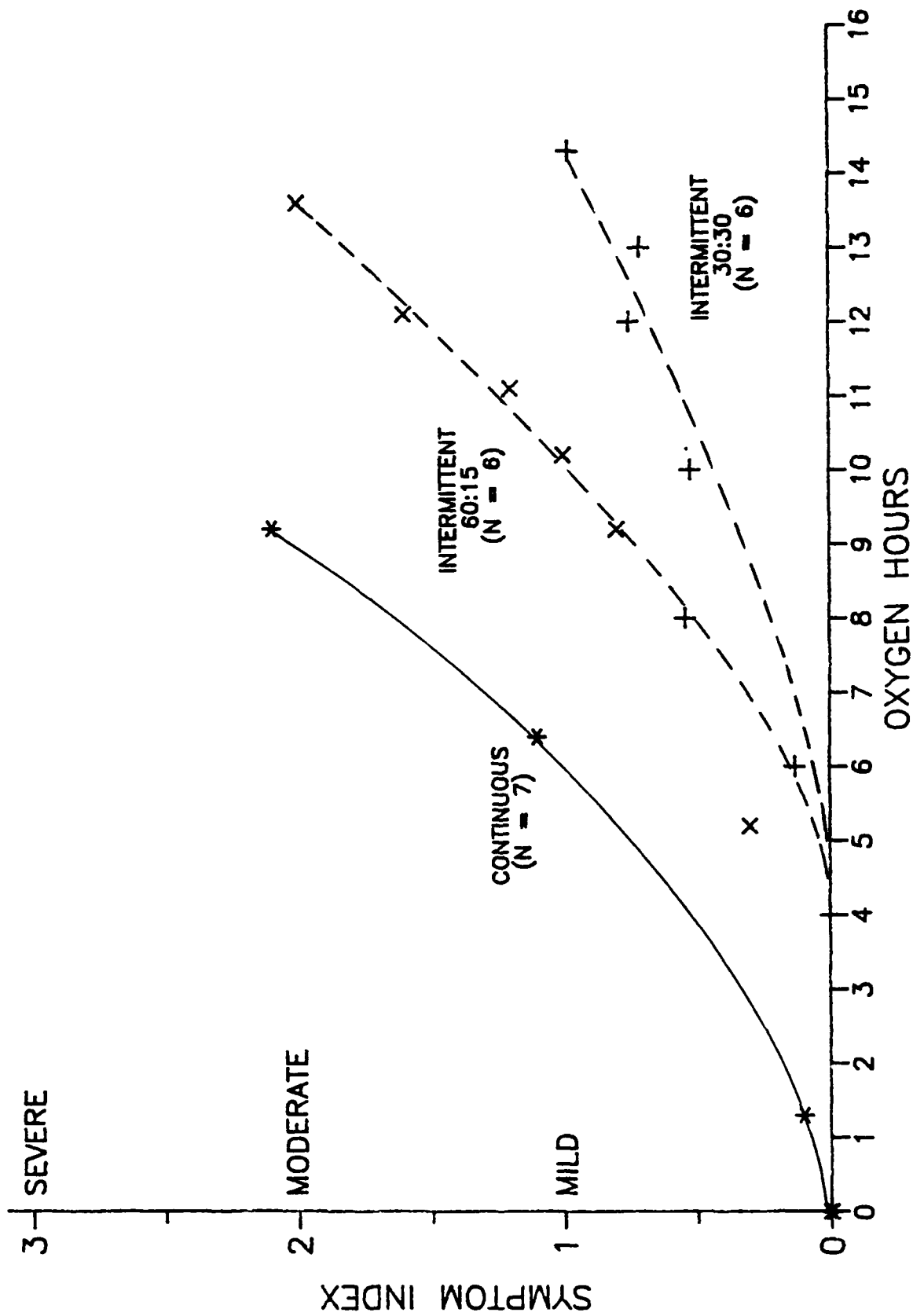
Appendix Figure 15

CHANGES IN ERG DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA



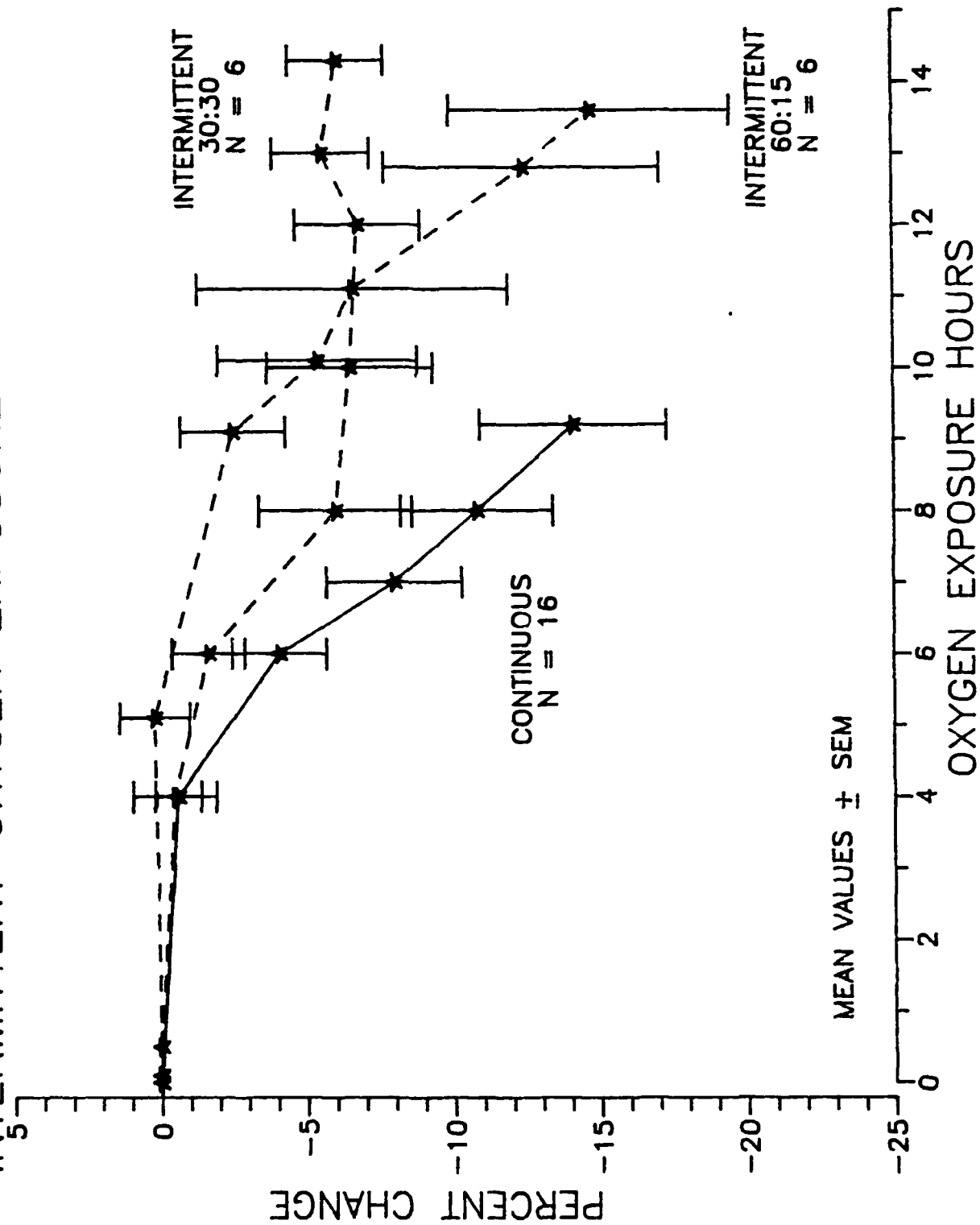
Appendix Figure 16

PULMONARY SYMPTOMS DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA IN MAN



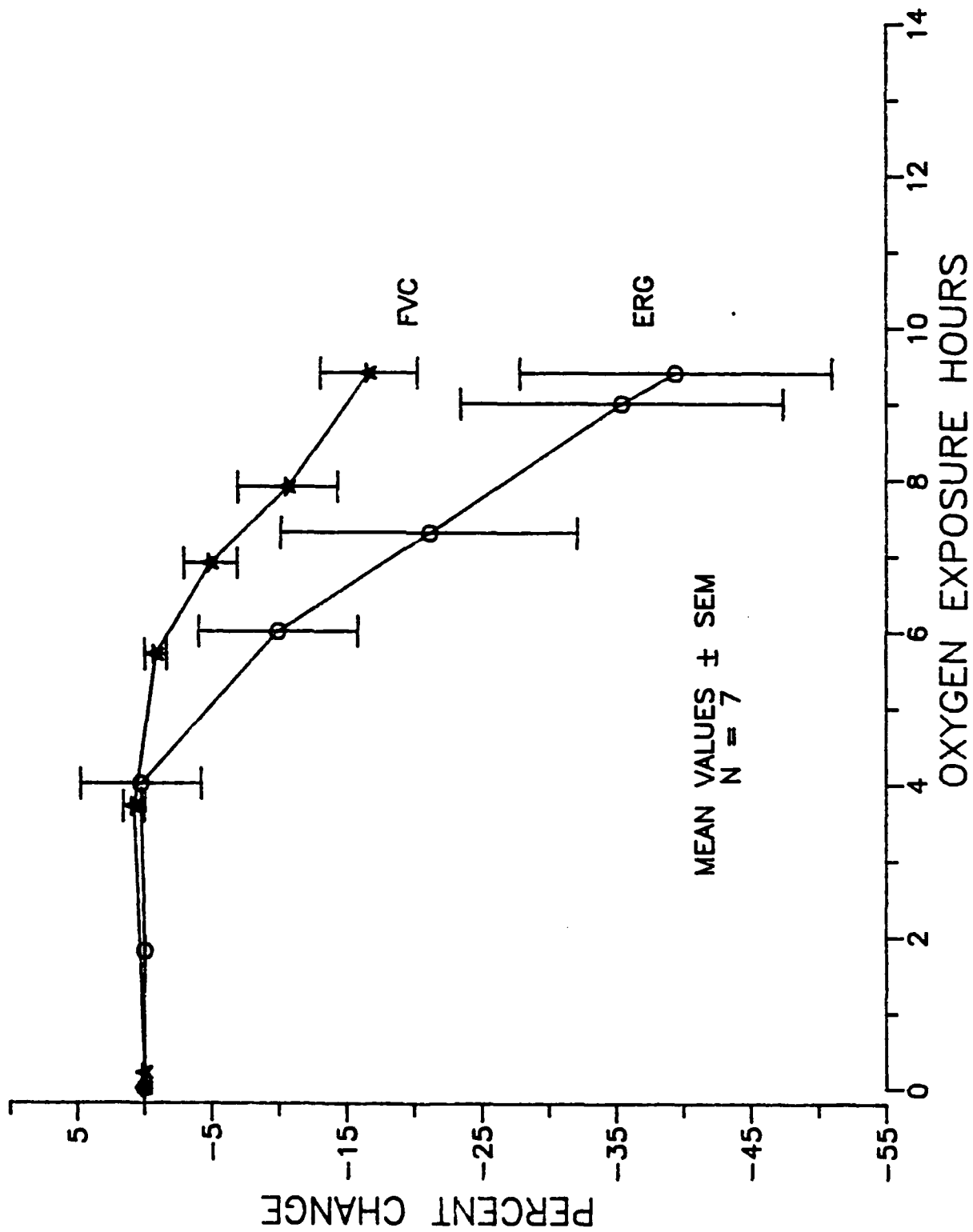
Appendix Figure 17

CHANGES IN FVC DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA



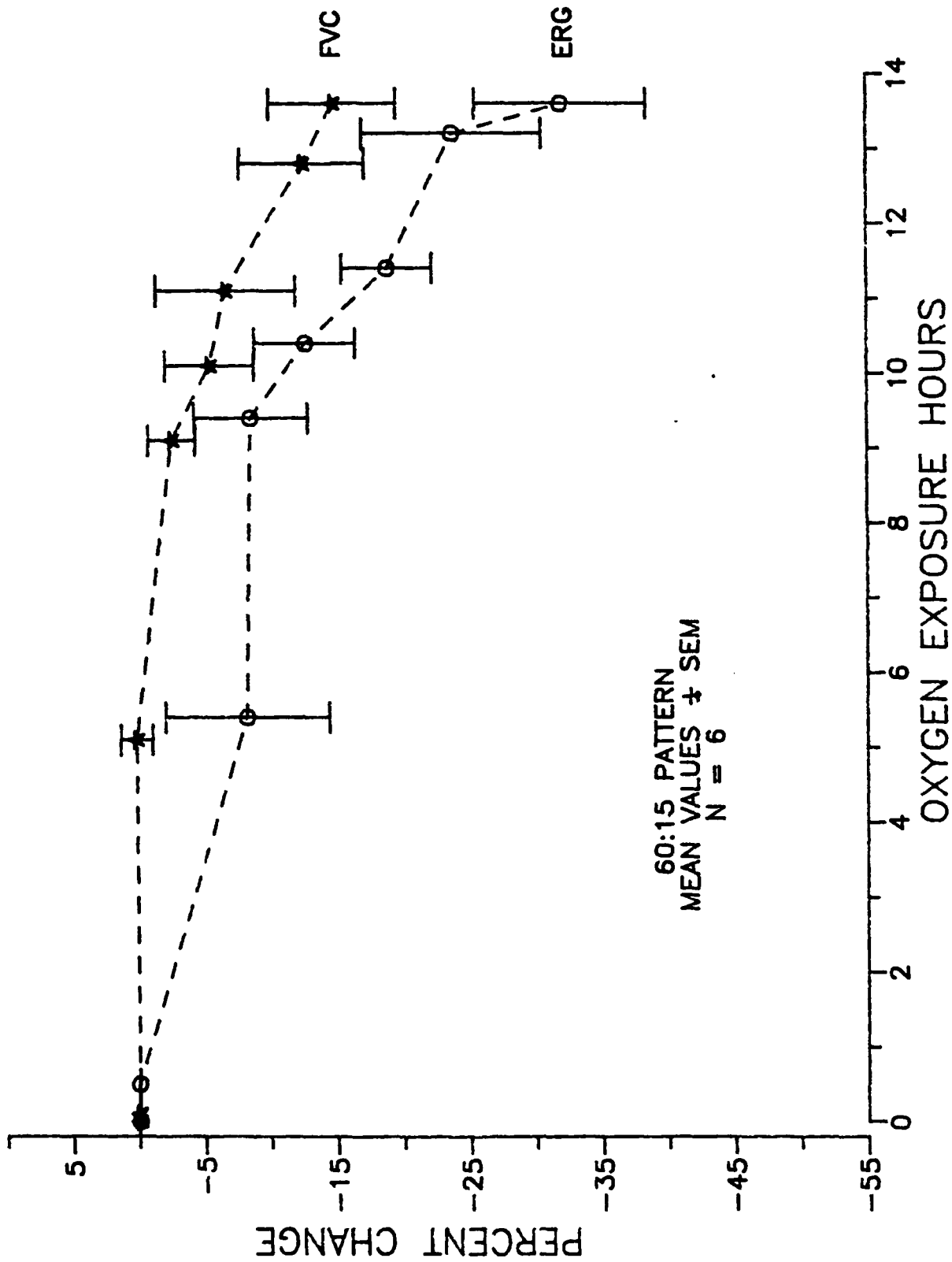
Appendix Figure 18

CHANGES IN ERG AND FVC DURING CONTINUOUS OXYGEN EXPOSURE AT 2.0 ATA



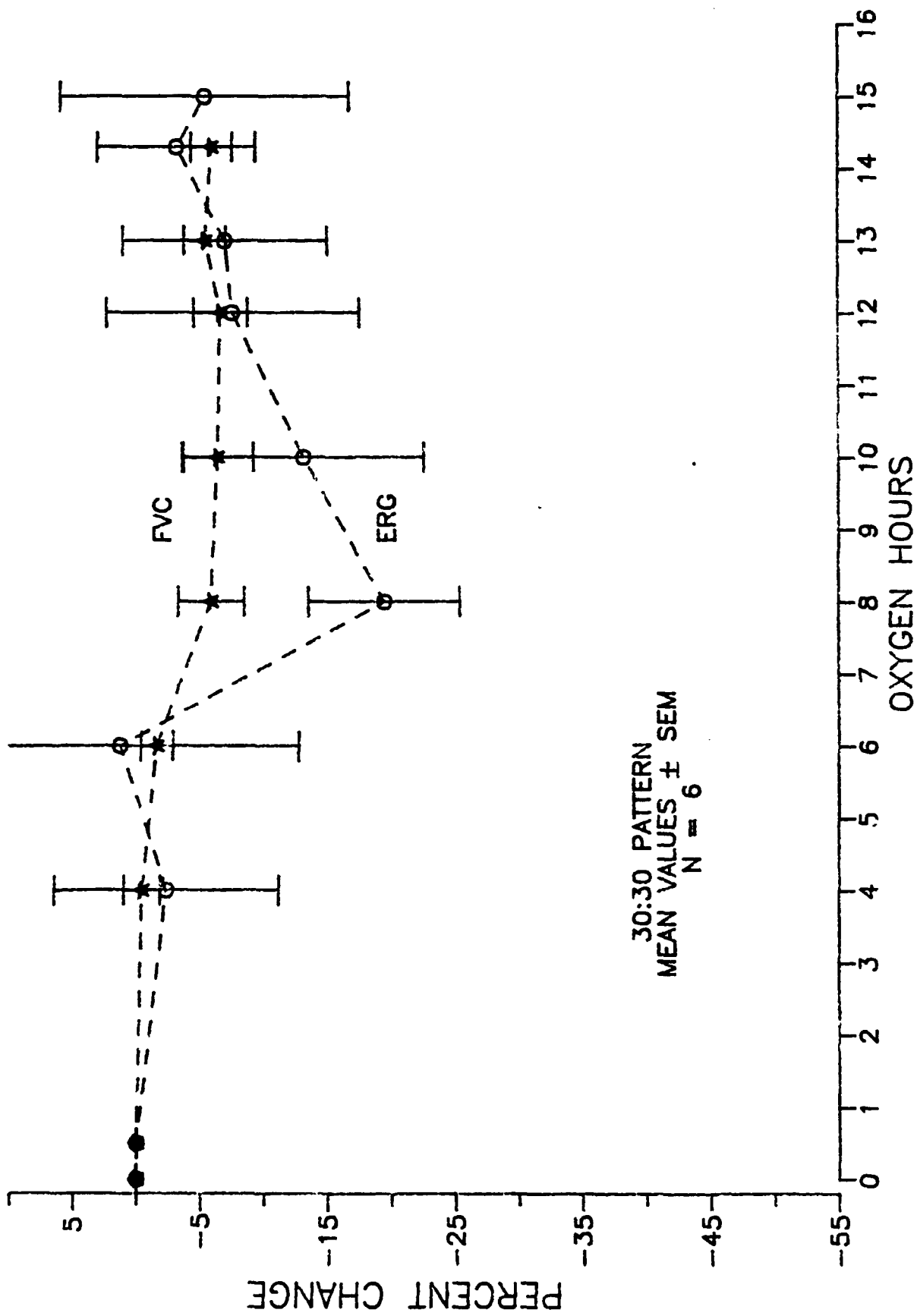
Appendix Figure 19

CHANGES IN ERG AND FVC DURING INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA

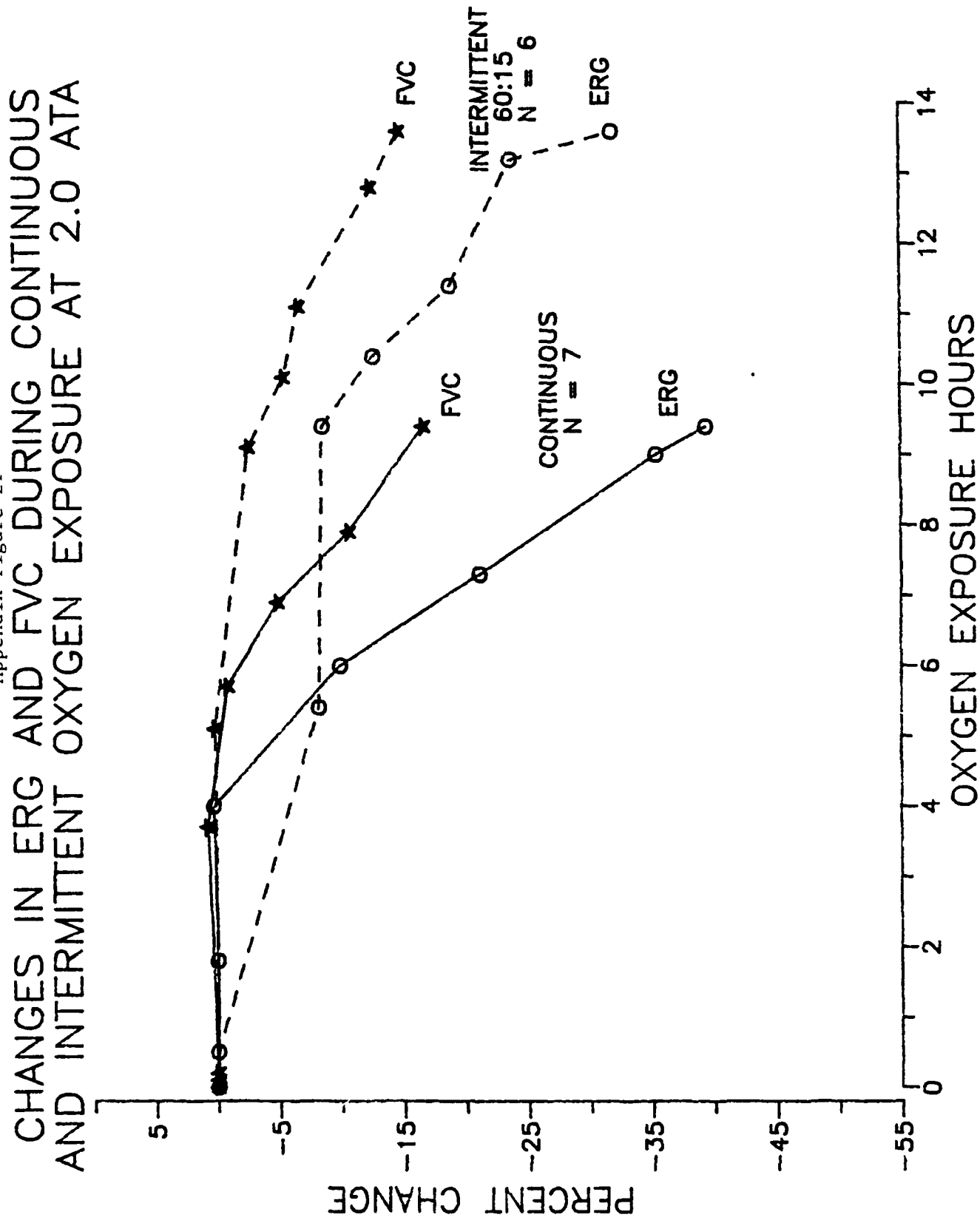


Appendix Figure 20

CHANGES IN ERG AND FVC DURING INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA

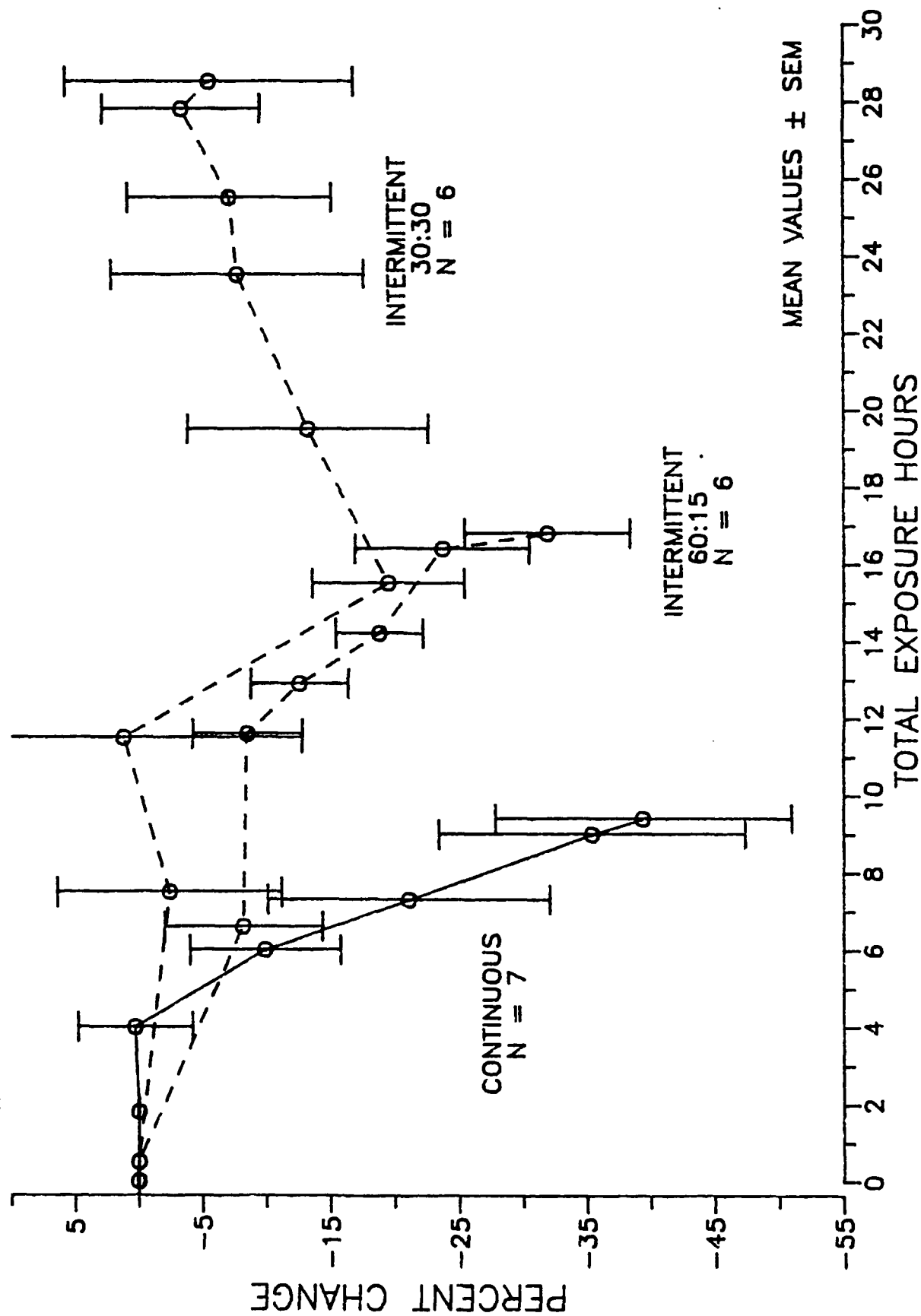


Appendix Figure 21



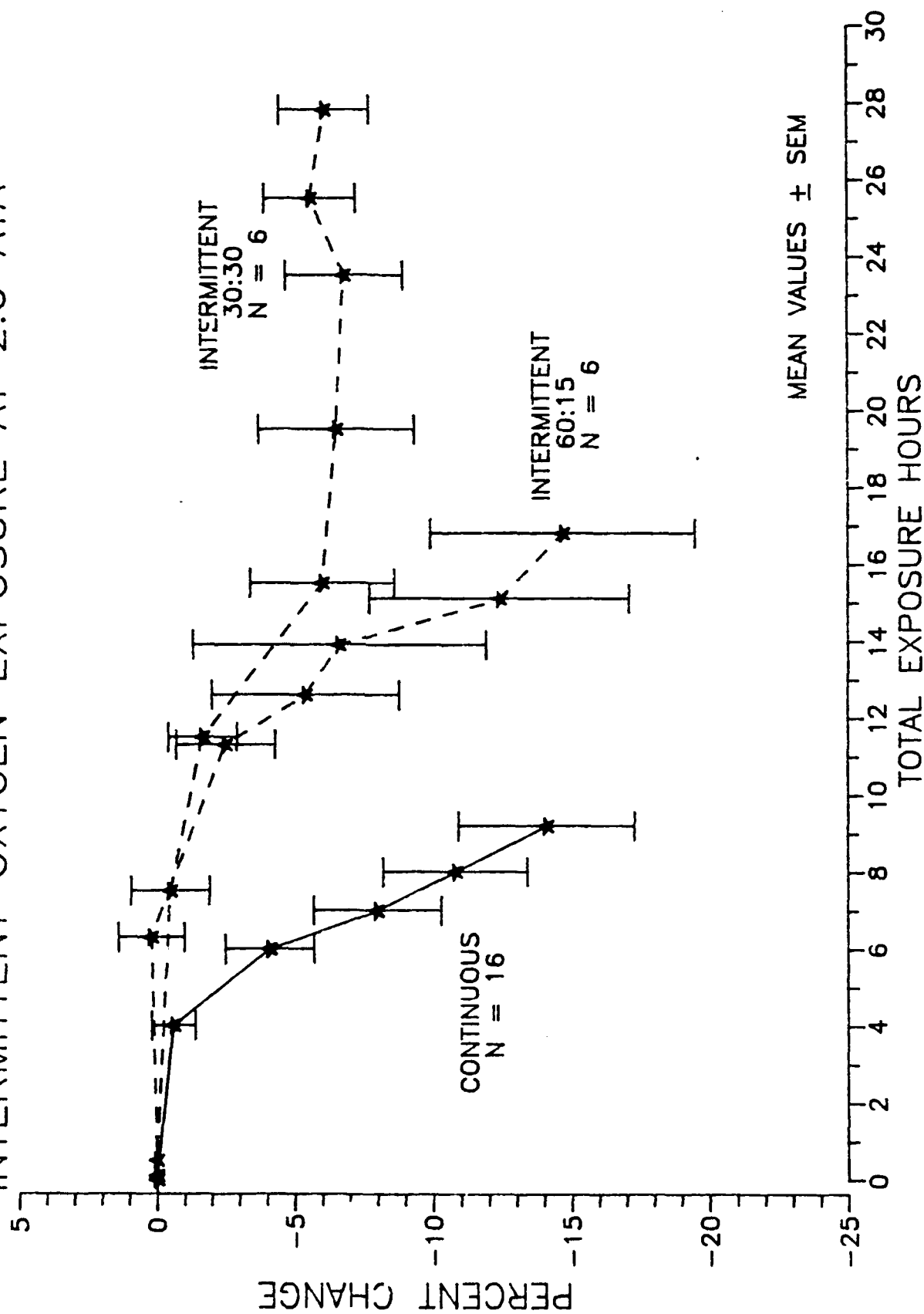
Appendix Figure 22

CHANGES IN ERG DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA



Appendix Figure 23

CHANGES IN FVC DURING CONTINUOUS AND INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA



Appendix Table 1

INTERMITTENT OXYGEN EXPOSURE PATTERNS FOR
OPTIMIZATION OF OXYGEN TOLERANCE EXTENSION IN RATS

O ₂ EXPOSURE (ATA) (Min)		NORMOXIC INTERVAL (Minutes)							
		5	10	15	20	30	60	120	180
4.0	20	X	X		X				
	60			X		X	X		X
	120					X	X	X	
2.0	20	X	X		X				
	60			X		X	X		X
	120					X	X	X	
1.5	20	X	X						
	60			X		X			
	120					X	X	X	

Appendix Table 2

INCREASE IN MEDIAN SURVIVAL TIME WITH INCREASING DURATION OF
NORMOXIC INTERVAL DURING INTERMITTENT OXYGEN EXPOSURE IN RATS

O ₂ EXPOSURE (ATA) (Min)		SLOPE OF MEDIAN SURVIVAL TIME INCREMENT (Hours per Minute of Normoxic Interval)
4.0	20	0.14
	60	0.04
	120	0.02
2.0	20	1.31
	60	0.03
	120	0.10
1.5	20	1.64
	60	0.42
	120	0.18

Appendix Table 3

EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON MENTAL PERFORMANCE AND PSYCHOMOTOR FUNCTION IN MAN 60:15 OXYGEN:NORMOXIC SEQUENCE

	PRE EXP 1 ATA	START EXP 2 ATA	END EXP 2 ATA	POST EXP 1 ATA	DIFFERENCES END- START 2 ATA	POST- PRE 1 ATA
Visual Digit Span Test Of Short Term Memory Ability (Correct Responses)						
N	7	7	7	6	7	6
MEAN	34.4	33.4	34.6	33.8	1.1	-1.0
SD	5.9	4.9	6.4	8.8	7.7	8.1
SEM	2.2	1.9	2.4	3.6	2.9	3.3
N	6	6	6	5	6	5
MEAN	33.0	33.7	33.3	32.6	-0.3	-0.6
SD	4.9	5.4	6.0	9.3	7.3	9.0
SEM	2.0	2.2	2.4	4.2	3.0	4.0
Key Insertion Test Of Finger Dexterity Ability (Correct Responses)						
N	4	4	4	4	4	3
MEAN	38.5	42.5	41.3	31.3	-1.3	-4.3
SD	9.5	5.1	6.3	5.7	6.8	15.0
SEM	4.7	2.5	3.2	3.3	3.4	8.6
Operations Test Of Number Facility And General Reasoning Ability [Correct Responses - 1/3 (Incorrect Responses)]						
N	7	7	7	7	7	7
MEAN	39.3	44.1	44.2	42.2	0.1	2.9
SD	9.4	6.2	7.6	7.3	5.3	9.8
SEM	3.5	2.4	2.9	2.8	2.0	3.7
N	6	6	6	6	6	6
MEAN	39.2	44.2	43.7	41.8	-0.5	2.6
SD	10.2	6.8	8.2	7.9	5.5	10.7
SEM	4.2	2.8	3.3	3.2	2.3	4.4
Visual Reaction Time Test Of Response Speed Ability (Seconds)						
N	7	7	7	7	7	7
MEAN	0.283	0.282	0.322	0.336	0.040	0.053
SD	0.029	0.036	0.067	0.080	0.045	0.060
SEM	0.011	0.014	0.025	0.030	0.017	0.023
N	6	6	6	6	6	6
MEAN	0.289	0.292	0.339	0.347	0.047*	0.059
SD	0.027	0.026	0.055	0.081	0.045	0.064
SEM	0.011	0.011	0.022	0.033	0.018	0.026

* Difference from control statistically significant by paired t-test
($p \leq 0.05$).

Appendix Table 4 (1 of 2)

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON VISUAL FUNCTION IN MAN
60:15 OXYGEN:NORMOXIC SEQUENCE**

	PRE EXP 1 ATA	START EXP 2 ATA	END EXP 2 ATA	POST EXP 1 ATA	DIFFERENCES	
					END- START 2 ATA	POST- PRE 1 ATA
Visual Evoked Response (Latency, msec)						
N	7	7	7	7	7	7
MEAN	111.28	113.96	117.20	116.53	3.24	5.25
SD	9.63	6.90	7.80	10.76	7.71	12.83
SEM	3.64	2.61	2.95	4.07	2.91	4.85
N	6	6	6	6	6	6
MEAN	108.58	112.46	118.25	116.42	5.79*	7.83
SD	7.09	6.16	7.99	11.78	4.07	11.89
SEM	2.89	2.52	3.26	4.81	1.66	4.85
Accommodation (Nearpoint, cm)						
N	7	6	7	7	6	7
MEAN	11.65	12.52	12.75	12.52	0.66	0.87
SD	2.21	2.76	3.58	2.79	1.19	1.21
SEM	0.83	1.13	1.35	1.05	0.49	0.46
N	6	6	6	6	6	6
MEAN	11.74	12.52	13.18	12.75	0.66	1.00
SD	2.40	2.76	3.71	2.98	1.19	1.27
SEM	0.98	1.13	1.52	1.22	0.49	0.52
Pupil Diameter (mm)						
N	7	7	7	7	7	7
MEAN	4.1	4.3	4.2	4.1	-0.1	-0.1
SD	0.7	0.6	0.3	0.8	0.5	0.7
SEM	0.3	0.2	0.1	0.3	0.2	0.3
N	6	6	6	6	6	6
MEAN	4.2	4.3	4.3	4.1	0.0	-0.1
SD	0.8	0.7	0.3	0.9	0.5	0.7
SEM	0.3	0.3	0.1	0.4	0.2	0.3

* Difference from control statistically significant by paired t-test (p ≤ 0.05).

Appendix Table 4 (2 of 2)

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON VISUAL FUNCTION IN MAN
60:15 OXYGEN:NORMOXIC SEQUENCE**

Visual Acuity

	PRE EXPOSURE 1 ATA	START EXPOSURE 2 ATA	END EXPOSURE 2 ATA	POST EXPOSURE 1 ATA
HK	20/20	20/25	20/20	20/25
KC	20/20	20/20	20/25	20/20
MM	20/20	20/20	20/25	20/20
RI	20/25	20/25	20/25	20/25
MB	20/25	20/25	20/20	20/20
GZ	20/20	20/20	20/20	20/20
AI	20/20	20/20	20/20	20/20

Appendix Table 5

PERIPHERAL VISUAL FIELD AREA DURING INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
60:15 OXYGEN:NORMOXIC SEQUENCE

	PRE EXP 1 ATA	START EXP 2 ATA	OXYGEN EXPOSURE HOURS						END EXP 2 ATA	POST EXP 1 ATA	
			5.2	9.2	10.2	11.2	12.2	13.2			14.2
Relative Area (% Control)											
N	7	7	6	6	6	6	4	3	7	7	
MEAN	100	100	95.4	94.1	89.7	86.1	93.0	95.8	99.8	92.3	
SD			4.4	7.7	8.0	9.1	8.2	2.2	8.1	13.1	
SEM			1.7	3.1	3.3	3.7	4.1	1.3	4.6	5.0	
N	6	6	6	6	6	6			6	6	
MEAN	100	100	95.2	94.1	89.7	86.1#			91.6*	91.6	
SD			4.8	7.7	8.0	9.1			10.9	14.2	
SEM			1.9	3.1	3.3	3.7			4.5	5.8	

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).

Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 6

ELECTRORETINOGRAM b-WAVE AMPLITUDE DURING INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
60:15 OXYGEN:NORMOXIC SEQUENCE

----- OXYGEN EXPOSURE HOURS -----													DIFFERENCES		
	PRE EXP 1 ATA	START EXP 2 ATA	5.4	9.4	10.4	11.4	12.4	13.4	14.4	END EXP 2 ATA	POST EXP 1 ATA	END- START 2 ATA	POST- PRE 1 ATA		
Responses to Light Intensity of 0.034 Foot Candles (Amplitude, mv)															
N	7	7	7	6	6	6	4	3	3	7	7	7	7		
MEAN	373.2	342.0	307.3	334.7	326.8	287.9	249.6	249.9	207.1	254.6	242.4	-87.3*	-130.7*		
SD	46.8	78.3	119.3	113.6	85.7	65.0	91.6	47.4	21.8	69.2	55.1	72.3	65.2		
SEM	17.7	29.6	45.1	46.4	35.0	26.5	45.8	27.3	12.6	26.2	20.8	27.3	24.6		
N	6	6	6	6	6	6				6	6	6	6		
MEAN	385.4	355.4	329.0	334.7	326.8	287.9				263.0	240.4	-92.4*	-144.9*		
SD	37.2	76.4	114.5	113.6	85.7	65.0				71.8	60.1	77.8	58.3		
SEM	15.2	31.2	46.8	46.4	35.0	26.5				29.3	24.5	31.8	23.8		
Responses To Light Intensity Of 0.065 Foot Candles (Amplitude, mv)															
N	7	7	7	6	6	6	4	3	3	7	7	7	7		
MEAN	386.2	371.0	338.1	366.4	333.6	330.2	292.9	347.5	253.7	282.7	292.7	-88.3*	-93.5*		
SD	61.9	75.6	128.1	89.2	107.6	74.2	108.2	78.1	59.9	66.0	67.8	59.4	98.3		
SEM	23.4	28.6	48.4	36.4	43.9	30.3	54.1	45.1	34.6	25.0	25.6	22.4	37.2		
N	6	6	6	6	6	6				6	6	6	6		
MEAN	400.6	385.9	361.5	366.4	333.6	330.2				289.5	294.9	-96.4*	-105.7		
SD	53.4	70.7	122.9	89.2	107.6	74.2				69.7	74.0	60.6	101.7		
SEM	21.8	28.9	50.2	36.4	43.9	30.3				28.4	30.2	24.7	41.5		
Responses To Light Intensity Of 0.163 Foot Candles (Amplitude, mv)															
N	7	7	7	6	6	6	4	3	3	7	7	7	7		
MEAN	397.8	384.9	350.2	357.3	348.7	305.8	288.2	258.6	273.7	296.6	278.3	-88.3*	-119.5*		
SD	58.8	88.6	128.6	100.7	98.6	56.6	85.6	82.6	94.4	72.3	67.0	89.7	52.8		
SEM	22.2	33.5	48.6	41.1	40.2	23.1	42.8	47.7	54.5	27.3	25.3	33.9	20.0		
N	6	6	6	6	6	6				6	6	6	6		
MEAN	409.6	401.7	380.1	357.3	348.7	305.8#				306.0	276.7	-95.6	-132.9*		
SD	54.6	83.9	111.0	100.7	98.6	56.6				74.2	73.2	95.9	42.8		
SEM	22.3	34.3	45.3	41.1	40.2	23.1				30.3	29.9	39.2	17.5		

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 7 (1 of 2)

VENTILATORY RESPONSES TO INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
60:15 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS						DIFFERENCES			

		PRE		START		END		POST		END-POST-	
		EXP 1 ATA	2 ATA	EXP 2 ATA	2 ATA	EXP 2 ATA	2 ATA	EXP 1 ATA	1 ATA	START 2 ATA	PRE 1 ATA
Expiratory Minute Volume (L/min)											

		5.6	9.6	10.6	11.6	12.6	13.6	14.6			
N	6	7	6	6	6	4	3	3	5	7	5
MEAN	6.94	9.25	8.27	10.30	11.10	9.62	9.86	10.99	8.47	1.13	1.69
SD	1.35	1.48	0.92	1.70	1.70	1.63	1.41	0.56	1.28	2.02	1.92
SEM	0.55	0.56	0.38	0.69	0.70	0.81	0.81	0.32	0.57	0.76	0.86
Respiratory Rate (Breaths/min)											

		5.6	9.6	10.6	11.6	12.6	13.6	14.6			
N	5	6	6	6	6				5	6	5
MEAN	6.78	9.04	8.27	10.30	11.10#				8.47	1.63	1.69
SD	1.44	1.50	0.92	1.70	1.70				1.28	1.66	1.92
SEM	0.65	0.61	0.38	0.69	0.70				0.57	0.68	0.86
Tidal Volume (L)											

		5.6	9.6	10.6	11.6	12.6	13.6	14.6			
N	6	7	6	6	6	4	2	3	5	7	7
MEAN	0.50	0.56	0.53	0.55	0.51	0.47	0.49	0.54	0.36	-0.06	-0.12
SD	0.10	0.07	0.06	0.16	0.03	0.06	0.05	0.07	0.08	0.10	0.12
SEM	0.04	0.03	0.02	0.07	0.01	0.03	0.03	0.04	0.04	0.04	0.05
Differences											

		5.6	9.6	10.6	11.6	12.6	13.6	14.6			
N	5	6	6	6	6				5	6	5
MEAN	0.48	0.56	0.52	0.55	0.51				0.36	-0.05	-0.12
SD	0.10	0.08	0.06	0.16	0.03				0.08	0.10	0.12
SEM	0.04	0.03	0.03	0.07	0.01				0.04	0.04	0.05

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 7 (2 of 2)

VENTILATORY RESPONSES TO INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
60:15 OXYGEN:NORMOXIC SEQUENCE

			OXYGEN EXPOSURE HOURS					Rate Of CO ₂ Elimination (L/min)					DIFFERENCES		
			-----					-----							
PRE EXP 1 ATA	START EXP 2 ATA		5.6	9.6	10.6	11.6	12.6	13.6	14.6	END EXP 2 ATA	POST EXP 1 ATA	END- START 2 ATA	POST- PRE 1 ATA		
Rate Of CO ₂ Elimination (L/min)															
N	6	7	6	6	6	6	4	2	3	7	5	7	5		
MEAN	0.20	0.23	0.20	0.20	0.22	0.23	0.21	0.20	0.21	0.22	0.21	-0.01	0.02		
SD	0.04	0.03	0.02	0.02	0.03	0.03	0.02	0.03	0.01	0.03	0.03	0.03	0.03		
SEM	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.01	0.01		
N	5	6	6	6	6	6				6	5	6	5		
MEAN	0.20	0.22	0.20#	0.20	0.22	0.23				0.23	0.21	0.01	0.02		
SD	0.04	0.04	0.02	0.02	0.03	0.03				0.03	0.03	0.02	0.03		
SEM	0.02	0.01	0.01	0.01	0.01	0.01				0.01	0.01	0.01	0.01		
End-Tidal PCO ₂ (mm Hg)															
N	7	7	6	6	6	6	4	2	3	7	6	7	6		
MEAN	40.8	33.6	32.6	33.4	32.5	31.8	31.4	29.7	28.6	30.4	36.2	-3.2*	-4.6*		
SD	2.8	1.9	1.7	1.9	2.2	2.4	1.7	3.7	2.0	2.4	3.3	2.9	3.3		
SEM	1.1	0.7	0.7	0.8	0.9	1.0	0.9	2.6	1.1	0.9	1.3	1.1	1.4		
N	6	6	6	6	6	6				6	5	6	5		
MEAN	40.9	33.9	32.8	33.4	32.5	31.8				30.1	36.1	-3.9*	-4.8*		
SD	3.1	1.9	1.9	1.9	2.2	2.4				2.4	3.7	2.6	3.7		
SEM	1.3	0.8	0.8	0.8	0.9	1.0				1.0	1.6	1.0	1.6		

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 8 (1 of 2)

EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON PULMONARY FUNCTION IN MAN
60:15 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS										DIFFERENCES						
		5.1		9.1		10.1		11.1		12.1		13.1		14.1				
PRE EXP 1 ATA	START EXP 2 ATA	Forced Vital Capacity (L)														END- START 2 ATA	POST- START 2 ATA	POST- PRE 1 ATA
N	7	7	6	6	6	6	6	6	6	4	3	3	3	7	7	7	7	
MEAN	5.33	5.10	5.03	4.85	4.71	4.63	4.82	4.68	4.54	4.61	4.53	4.80	4.63	-0.49	-0.57	-0.53*	-0.53*	
SD	0.48	0.59	0.47	0.56	0.64	0.74	0.36	0.24	0.71	0.92	0.97	0.66	0.61	0.67	0.76	0.41	0.41	
SEM	0.18	0.22	0.18	0.23	0.26	0.30	0.18	0.14	0.41	0.35	0.37	0.25	0.25	0.25	0.29	0.15	0.15	
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
MEAN	5.22	4.97	4.98	4.85	4.71	4.63	4.71	4.68	4.54	4.34	4.22	4.63	4.63	-0.63	-0.76*	-0.59*	-0.59*	
SD	0.40	0.51	0.49	0.56	0.64	0.74	0.36	0.24	0.71	0.63	0.54	0.53	0.53	0.61	0.65	0.42	0.42	
SEM	0.16	0.21	0.20	0.23	0.26	0.30	0.18	0.14	0.41	0.26	0.22	0.22	0.22	0.25	0.27	0.17	0.17	
One Second Forced Expired Volume (L)																		
N	7	7	6	6	6	6	6	6	6	4	3	3	3	7	7	7	7	
MEAN	4.35	3.64	3.59	3.34	3.19	3.23	3.45	3.16	3.21	3.34	3.31	3.83	3.83	-0.30	-0.33	-0.52*	-0.52*	
SD	0.51	0.57	0.57	0.58	0.69	0.66	0.49	0.06	0.28	0.65	0.71	0.40	0.40	0.45	0.55	0.37	0.37	
SEM	0.19	0.22	0.22	0.24	0.28	0.27	0.24	0.03	0.16	0.25	0.27	0.15	0.15	0.17	0.21	0.14	0.14	
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
MEAN	4.29	3.56	3.51	3.34	3.19	3.23	3.45	3.16	3.21	3.19	3.15	3.77	3.77	-0.38	-0.42	-0.52*	-0.52*	
SD	0.54	0.58	0.59	0.58	0.69	0.66	0.49	0.06	0.28	0.57	0.61	0.41	0.41	0.45	0.54	0.40	0.40	
SEM	0.22	0.24	0.24	0.24	0.28	0.27	0.24	0.03	0.16	0.23	0.25	0.17	0.17	0.18	0.22	0.16	0.16	

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 8 (2 of 2)

EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON PULMONARY FUNCTION IN MAN
60:15 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS					-----				DIFFERENCES			
	PRE EXP 1 ATA	START EXP 2 ATA	5.1	9.1	10.1	11.1	12.1	13.1	14.1	END EXP 2 ATA	Peak Expiratory Flow Rate (L/sec)			
											POST EXP 2 ATA	POST EXP 1 ATA	END- START 2 ATA	POST- START 2 ATA

N	7	7	7	6	6	6	4	3	3	7	7	7	7	7
MEAN	9.96	6.82	6.47	6.12	5.57	5.68	6.46	5.52	5.99	5.95	6.09	8.34	-0.87	-0.73
SD	1.52	0.80	1.25	1.62	1.78	0.97	1.98	1.13	1.28	1.17	1.76	1.24	1.05	1.09
SEM	0.57	0.30	0.47	0.66	0.73	0.40	0.99	0.65	0.74	0.44	0.67	0.47	0.40	0.41

N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
MEAN	9.93	6.70	6.41	6.12	5.57	5.68	6.46	5.52	5.99	5.69	5.92	8.39	-1.01	-0.78
SD	1.66	0.80	1.36	1.62	1.78	0.97	1.98	1.13	1.28	1.03	1.87	1.35	1.08	1.19
SEM	0.68	0.33	0.56	0.66	0.73	0.40	0.99	0.65	0.74	0.42	0.76	0.55	0.44	0.48

Maximal Mid-Expiratory Flow Rate (L/sec)														
N	7	7	7	6	6	6	4	3	3	7	7	7	7	7
MEAN	4.53	2.86	2.86	2.65	2.42	2.51	2.79	2.26	2.46	2.72	2.78	3.81	-0.13	-0.08
SD	1.46	0.96	0.96	0.79	0.89	0.91	1.16	0.34	0.17	0.88	1.01	1.09	0.45	0.50
SEM	0.55	0.36	0.36	0.32	0.36	0.37	0.58	0.20	0.10	0.33	0.38	0.41	0.17	0.19

N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
MEAN	4.60	2.83	2.77	2.65	2.42	2.51	2.73	2.42	2.66	2.66	2.73	3.94	-0.17	-0.10
SD	1.59	1.04	1.01	0.79	0.89	0.91	1.10	0.94	0.94	0.94	1.10	1.14	0.48	0.55
SEM	0.65	0.43	0.41	0.32	0.36	0.37	0.45	0.39	0.39	0.39	0.45	0.46	0.20	0.22

* Difference from control statistically significant ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 9 (1 of 2)

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON PULMONARY FUNCTION IN MAN
60:15 OXYGEN:NORMOXIC SEQUENCE**

	PRE EXP	POST EXP	POST- PRE Δ	PRE EXP	POST EXP	POST- PRE Δ
	Slow Vital Capacity (L)			Inspiratory Capacity (L)		
N	7	7	7	7	7	7
MEAN	5.35	4.80	-0.54*	3.49	2.86	-0.63*
SD	0.56	0.65	0.45	0.52	0.83	0.41
SEM	0.21	0.25	0.17	0.20	0.31	0.16
N	6	6	6	6	6	6
MEAN	5.20	4.62	-0.59*	3.38	2.66	-0.72*
SD	0.45	0.46	0.47	0.47	0.70	0.37
SEM	0.18	0.19	0.19	0.19	0.28	0.15
	Expiratory Reserve Volume (L)			Total Lung Capacity (L)		
N	7	7	7	7	7	7
MEAN	1.85	1.95	0.09	6.13	5.48	-0.65*
SD	0.38	0.39	0.23	0.70	0.82	0.40
SEM	0.14	0.15	0.09	0.26	0.31	0.15
N	6	6	6	6	6	6
MEAN	1.82	1.96	0.14	6.02	5.34	-0.68*
SD	0.40	0.42	0.21	0.69	0.79	0.43
SEM	0.16	0.17	0.08	0.28	0.32	0.18

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).

Appendix Table 9 (2 of 2)

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON PULMONARY FUNCTION IN MAN
60:15 OXYGEN:NORMOXIC SEQUENCE**

	PRE EXP	POST EXP	POST- PRE Δ	PRE EXP	POST EXP	POST- PRE Δ
CO Diffusing Capacity (ml/CO/mm Hg/min)			Density Dependence of Flow (% Δ $\dot{V}_{max_{50}}$)			
N	7	7	7	6	6	6
MEAN	34.0	33.7	-0.3	43.7	35.3	-8.4
SD	4.1	4.1	2.0	9.3	20.0	24.0
SEM	1.5	1.5	0.7	3.8	8.2	9.8
N	6	6	6	5	5	5
MEAN	33.1	33.4	0.3	44.0	33.2	-10.8
SD	3.6	4.4	1.3	10.4	21.6	26.0
SEM	2.5	1.8	0.5	4.7	9.6	11.6
Airway Resistance (cm H ₂ O/L/sec)			Specific Lung Compliance (L/cm H ₂ O/L)			
N	7	7	7	7	7	7
MEAN	2.07	2.11	0.04	0.139	0.112	-0.028*
SD	0.40	0.52	0.20	0.032	0.032	0.023
SEM	0.15	0.20	0.07	0.012	0.012	0.009
N	6	6	6	6	6	6
MEAN	1.95	1.94	-0.01	0.144	0.114	-0.029*
SD	0.23	0.30	0.19	0.032	0.034	0.025
SEM	0.09	0.12	0.08	0.013	0.014	0.010

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).

Appendix Table 10

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON ARTERIAL OXYGENATION AND ACIP-BM/3 STATE IN MAN
60:15 OXYGEN:NORMOXIC SEQUENCE**

	PAO ₂ (mm Hg)	PaO ₂ (mm Hg)	Δ PO ₂ (mm Hg)	PCO ₂ (mm Hg)	pH	[HCO ₃] (meq/L)	PAO ₂ (mm Hg)	PaO ₂ (mm Hg)	Δ PO ₂ (mm Hg)	PCO ₂ (mm Hg)	pH	[HCO ₃] (meq/L)
At Rest Breathing Air At 1.0 ATA												
	PRE-EXPOSURE						POST-EXPOSURE					
N	5	5	5	5	5	5	5	5	5	5	5	5
MEAN	100.1	98.6	1.5	43.1	7.380	25.3	101.3	91.5	9.8	39.9*	7.396	23.6*
SD	6.5	4.0	9.8	4.2	0.032	1.3	8.0	10.8	11.5	4.1	0.039	1.8
SEM	2.9	1.8	4.4	1.9	0.014	0.6	3.6	4.8	5.1	1.8	0.018	0.8
During Exercise Breathing Air At 1.0 ATA												
	PRE-EXPOSURE						POST-EXPOSURE					
N	5	5	5	5	5	5	5	5	5	5	5	5
MEAN	105.5	97.7	7.8	42.6	7.357	23.5	111.0*	96.6	14.4	37.3*	7.389*	22.2
SD	5.6	3.7	6.4	5.3	0.038	1.8	6.4	7.5	12.0	5.0	0.031	1.9
SEM	2.5	1.6	2.9	2.4	0.017	0.8	2.9	3.4	5.3	2.2	0.014	0.8
At Rest Breathing Oxygen at 2.0 ATA												
	START EXPOSURE						END EXPOSURE					
N	5	4	4	5	5	5	5	4	4	5	5	5
MEAN	1438	1392	45	37.5	7.456	26.3	1438	1379	59	37.4	7.424*	24.1
SD	10	55	46	6.1	0.032	3.8	7	32	36	5.0	0.031	2.1
SEM	4	28	23	2.7	0.014	1.7	3	16	16	2.2	0.014	0.9

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).

Appendix Table 11

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON RESPIRATORY AND SKELETAL MUSCLE STRENGTH
60:15 OXYGEN:NORMOXIC SEQUENCE**

	PRE EXP	POST EXP	POST- PRE Δ	PRE EXP	POST EXP	POST- PRE Δ
Maximum Inspiratory Pressure (cm H₂O)						
	At Residual Volume			At Functional Residual Capacity		
N	7	7	7	7	7	7
MEAN	134.3	109.2	-25.1	119.3	99.8	-19.4
SD	41.3	34.5	42.0	49.5	33.3	44.9
SEM	15.6	13.0	15.9	18.7	12.6	17.0
N	6	6	6	6	6	6
MEAN	144.1	113.5	-30.6	126.8	104.1	-22.7
SD	35.3	35.7	43.2	49.6	34.4	48.2
SEM	14.4	14.6	17.6	20.2	14.0	19.7
Maximum Expiratory Pressure (cm H₂O)						
	At Total Lung Capacity			At Functional Residual Capacity		
N	7	7	7	7	7	7
MEAN	127.9	110.6	-17.4	124.0	96.4	-27.6
SD	41.8	30.9	33.7	42.7	43.6	48.0
SEM	15.8	11.7	12.8	16.1	16.5	18.1
N	6	6	6	6	6	6
MEAN	133.8	111.6	-22.2	131.7	97.2	-34.6
SD	42.6	33.7	34.2	41.0	47.8	48.5
SEM	17.4	13.8	14.0	16.8	19.5	19.8
	Maximum Handgrip Strength (Kg)			Duration for 80% Maximum Handgrip (Sec)		
N	7	7	7	7	7	7
MEAN	51.4	49.6	-1.7	31.2	23.6	-7.6
SD	4.2	8.0	6.7	18.6	18.6	9.5
SEM	1.6	3.0	2.5	7.0	7.0	3.6
N	6	6	6	6	6	6
MEAN	51.7	50.8	-0.8	35.3	26.5	-8.8
SD	4.5	8.0	6.8	16.6	18.5	9.9
SEM	1.8	3.3	2.8	6.8	7.6	5.0

* Difference from control significantly significant by paired t-test ($p \leq 0.05$).

Appendix Table 12 (1 of 2)

EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON CARDIOVASCULAR FUNCTION AND DEEP BODY TEMPERATURE IN MAN
60:15 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS										DIFFERENCES													
		START EXP 2 ATA		5.7		9.7		10.7		11.7		12.7		13.7		14.7		END EXP 2 ATA		POST EXP 1 ATA		END- START 2 ATA		POST- PRE 1 ATA	
		Heart Rate (Beats/min)																							
N	7	7	7	7	6	6	6	6	6	6	4	3	3	3	7	7	7	7	7	7	7	7	7	7	7
MEAN	56.7	48.4	48.9	51.5	55.2	55.3	55.3	57.8	61.7	61.3	61.3	61.3	61.3	61.3	57.3	58.4	58.4	8.9*	8.9*	8.9*	8.9*	8.9*	8.9*	8.9*	1.7
SD	6.4	3.2	4.1	2.9	6.6	3.1	4.8	3.2	3.2	5.0	5.0	5.0	5.0	5.0	6.1	9.3	9.3	5.8	5.8	5.8	5.8	5.8	5.8	5.8	12.5
SEM	2.4	1.2	1.5	1.2	2.7	1.3	2.4	1.9	1.9	2.9	2.9	2.9	2.9	2.9	2.3	3.5	3.5	2.2	2.2	2.2	2.2	2.2	2.2	2.2	4.7
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
MEAN	57.3	48.3	49.5	51.5	55.2#	55.3#	55.3#								59.0	60.2	60.2	10.7*	10.7*	10.7*	10.7*	10.7*	10.7*	10.7*	2.8
SD	6.8	3.5	4.1	2.9	6.6	3.1									4.5	8.8	8.8	3.7	3.7	3.7	3.7	3.7	3.7	3.7	13.3
SEM	2.8	1.4	1.7	1.2	2.7	1.3									1.8	3.6	3.6	1.5	1.5	1.5	1.5	1.5	1.5	1.5	5.4
Stroke Volume (ml)																									
N	7	7	7	7	6	6	6	6	6	6	4	3	3	3	7	7	7	7	7	7	7	7	7	7	7
MEAN	137.0	141.1	133.4	121.5	114.4	118.0	106.1	116.0	111.3	111.3	111.3	111.3	111.3	111.3	113.4	121.2	121.2	-27.7*	-27.7*	-27.7*	-27.7*	-27.7*	-27.7*	-27.7*	-15.9
SD	21.0	31.8	44.1	40.7	36.4	45.5	35.8	40.9	37.6	37.6	37.6	37.6	37.6	37.6	35.9	38.1	38.1	22.1	22.1	22.1	22.1	22.1	22.1	22.1	33.6
SEM	7.9	12.0	16.7	16.6	16.3	18.6	17.9	23.6	21.7	21.7	21.7	21.7	21.7	21.7	13.6	14.4	14.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4	12.7
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
MEAN	132.5	133.5	120.9	121.5	118.0	118.0									105.7	112.9	112.9	-27.7*	-27.7*	-27.7*	-27.7*	-27.7*	-27.7*	-27.7*	-19.6
SD	18.8	26.9	32.0	40.7	45.5	45.5									32.4	34.0	34.0	24.2	24.2	24.2	24.2	24.2	24.2	24.2	35.1
SEM	7.7	11.0	13.0	16.6	18.6	18.6									13.2	13.9	13.9	9.9	9.9	9.9	9.9	9.9	9.9	9.9	14.3
Cardiac Output (L/min)																									
N	7	7	7	7	6	6	6	6	6	6	4	3	3	3	7	7	7	7	7	7	7	7	7	7	7
MEAN	7.75	6.89	6.51	6.30	6.37	6.57	6.25	7.08	6.82	6.82	6.82	6.82	6.82	6.82	6.45	6.94	6.94	-0.44	-0.44	-0.44	-0.44	-0.44	-0.44	-0.44	-0.81
SD	1.31	1.78	2.09	2.28	2.34	2.65	2.59	2.13	2.32	2.32	2.32	2.32	2.32	2.32	1.99	1.94	1.94	1.52	1.52	1.52	1.52	1.52	1.52	1.52	1.73
SEM	0.49	0.67	0.79	0.93	1.05	1.08	1.29	1.23	1.34	1.34	1.34	1.34	1.34	1.34	0.75	0.73	0.73	0.58	0.58	0.58	0.58	0.58	0.58	0.58	0.66
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
MEAN	7.58	6.50	6.04	6.30	6.57	6.57									6.27	6.73	6.73	-0.23	-0.23	-0.23	-0.23	-0.23	-0.23	-0.23	-0.86
SD	1.35	1.60	1.82	2.28	2.65	2.65									2.12	2.04	2.04	1.56	1.56	1.56	1.56	1.56	1.56	1.56	1.89
SEM	0.55	0.66	0.74	0.93	1.08	1.08									0.86	0.83	0.83	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.77

*Difference from control statistically significant by paired t-test ($p \leq 0.05$).#Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 12 (2 of 2)

EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON CARDIOVASCULAR FUNCTION AND DEEP BODY TEMPERATURE IN MAN
60:15 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS -----										DIFFERENCES			
		PRE EXP 1 ATA	START EXP 2 ATA	5.7	9.7	10.7	11.7	12.7	13.7	14.7	END EXP 2 ATA	POST EXP 1 ATA	END- START 2 ATA	POST- PRE 1 ATA	
		Mean Arterial Blood Pressure (mm Hg)													
N	7	7	6	7	6	6	6	4	3	3	7	7	7	7	
MEAN	90.5	93.0	94.5	93.1	95.8	92.5	89.8	84.7	84.7	84.7	92.0	90.3	-1.0	-0.2	
SD	6.0	4.8	11.8	5.7	5.4	4.9	5.7	8.7	8.7	8.7	9.0	8.9	10.4	12.1	
SEM	2.3	1.8	4.5	2.3	2.2	2.0	2.9	3.3	5.0	5.0	3.4	3.4	3.9	4.6	
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
MEAN	91.0	93.4	96.2	93.1	95.8	92.5					90.1	89.5	-3.3	-1.5	
SD	6.4	5.1	12.1	5.7	5.4	4.9					8.2	9.5	9.3	12.7	
SEM	2.6	2.1	4.9	2.3	2.2	2.0					3.3	3.9	3.8	5.2	
Systemic Vascular Resistance (dyne sec/cm)															
N	7	7	7	6	5	6	4	3	3	3	7	7	7	7	
MEAN	11.98	14.34	15.97	16.84	16.81	15.99	16.41	13.63	14.05	14.05	15.75	14.34	1.41	2.37	
SD	2.24	3.83	5.68	7.05	5.58	5.97	6.63	4.75	7.23	7.23	5.73	6.14	4.05	6.07	
SEM	0.85	1.45	2.15	2.88	2.49	2.44	3.32	2.74	4.17	4.17	2.17	2.32	1.53	2.30	
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
MEAN	12.30	15.09	17.13	16.84	15.99	15.99					16.08	14.81	1.00	2.51	
SD	2.26	3.60	5.24	7.05	5.97	5.97					6.21	6.59	4.27	6.64	
SEM	0.92	1.47	2.14	2.88	2.44	2.44					2.53	2.69	1.74	2.71	

*Difference from control statistically significant by paired t-test ($p \leq 0.05$).#Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 13

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON MENTAL PERFORMANCE AND PSYCHOMOTOR FUNCTION IN MAN
30:30 OXYGEN:NORMOXIC SEQUENCE**

	PRE	START	END	POST	DIFFERENCES	
	EXP	EXP	EXP	EXP	END- START	POST- PRE
	1 ATA	2 ATA	2 ATA	1 ATA	2 ATA	1 ATA

**Visual Digit Span Test Of Short Term Memory Ability
(Correct Responses)**

N	6	6	6	6	6	6
MEAN	31.2	32.8	32.2	36.0	-0.7	4.8
SD	5.8	4.3	4.5	4.5	5.8	5.4
SEM	2.4	1.8	1.8	1.8	2.4	2.2

**Key Insertion Test of Finger Dexterity Ability
(Correct Responses)**

N	6	6	6	6	6	6
MEAN	62.7	52.8	52.7	49.2	-0.2	-13.5*
SD	4.3	11.5	8.0	10.2	9.2	7.5
SEM	1.8	4.7	3.3	4.2	3.8	3.1

**Operations Test of Number Facility and General Reasoning Ability
[Correct Responses - 1/3 (Incorrect Responses)]**

N	6	6	6	6	6	6
MEAN	69.5	68.6	72.2	69.6	3.6	0.1
SD	8.5	11.1	9.6	7.7	3.9	6.8
SEM	3.5	4.5	3.9	3.1	1.6	2.8

**Visual Reaction Time Test of Response Speed Ability
(Seconds)**

N	6	6	6	6	6	6
MEAN	0.283	0.304	0.292	0.318	-0.013	0.034
SD	0.017	0.027	0.032	0.047	0.021	0.037
SEM	0.007	0.011	0.013	0.019	0.009	0.015

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).

Appendix Table 14

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON VISUAL FUNCTION IN MAN
30:30 OXYGEN:NORMOXIC SEQUENCE**

	PRE EXP 1 ATA	START EXP 2 ATA	END EXP 2 ATA	POST EXP 1 ATA	DIFFERENCES	
					END- START 2 ATA	POST- PRE 1 ATA
Visual Evoked Response (Latency, msec)						
N	6			6		6
MEAN	108.73			108.42		-0.32
SD	3.48			8.69		6.91
SEM	1.42			3.55		2.82
Accommodation (Nearpoint, cm)						
N	6	6	6	6	6	6
MEAN	10.16	10.45	10.42	10.33	-0.03	0.17
SD	1.47	1.36	1.51	1.37	0.25	0.46
SEM	0.60	0.56	0.62	0.56	0.10	0.19
Pupil Diameter (mm)						
N	6	6	6	6	6	6
MEAN	3.9	4.6	4.5	3.9	-0.1	0.0
SD	0.9	0.7	0.7	0.8	1.1	0.4
SEM	0.4	0.3	0.3	0.3	0.5	0.1
Visual Acuity						
CS	20/30	20/30	20/30	20/30		
EK	20/25	20/25	20/30	20/30		
JB	20/20	20/20	20/20	20/20		
MS	20/20	20/20	20/20	20/20		
PS	20/20	20/20	20/20	20/20		
CK	20/25	20/25	20/25	20/25		

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).

Appendix Table 16

ELECTRORETINOGRAM b-WAVE AMPLITUDE DURING INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
30:30 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS										DIFFERENCES				
		PRE EXP 1 ATA		START EXP 2 ATA		4.0	6.0	8.0	10.0	12.0	13.0	14.0	END EXP 2 ATA	POST EXP 1 ATA	END- START 2 ATA	POST- PRE 1 ATA
Responses to Light Intensity of 0.034 Foot Candles (Amplitude, mv)																
N	6	6	6	6	6	6	6	6	6	6	6	4	6	6	6	6
MEAN	390.7	350.5	367.2	351.3	288.8	297.6	336.9	324.4	331.6	338.4	328.6	338.4	328.6	328.6	-12.1	-62.1
SD	172.9	80.0	101.7	110.0	59.2	52.3	98.3	98.2	124.4	116.1	110.5	116.1	110.5	110.5	77.6	100.2
SEM	70.6	32.6	41.5	44.9	24.2	21.4	40.1	40.1	62.2	47.4	45.1	62.2	47.4	45.1	31.7	40.9
Responses To Light Intensity Of 0.065 Foot Candles (Amplitude, mv)																
N	6	6	6	6	6	6	6	6	6	6	6	4	6	6	6	6
MEAN	421.7	404.3	358.1	374.3	296.0#	326.4	360.4	343.0	331.5	370.6	358.5	331.5	370.6	358.5	-33.7*	-63.2
SD	159.9	89.7	74.5	113.8	78.4	62.5	94.8	82.7	91.7	103.7	121.7	91.7	103.7	121.7	28.6	101.8
SEM	65.3	36.6	30.4	46.5	32.0	25.5	38.7	33.8	45.9	42.4	49.7	45.9	42.4	49.7	11.7	41.6
Responses To Light Intensity Of 0.163 Foot Candles (Amplitude, mv)																
N	6	6	6	6	6	6	6	6	6	6	6	4	6	6	6	6
MEAN	402.4	403.5	378.6	413.0	337.3	349.0	360.6	397.1	377.0	424.0	414.5	377.0	424.0	414.5	20.5	12.1
SD	122.2	94.4	60.7	108.2	89.5	70.4	129.2	91.5	114.8	139.9	126.0	114.8	139.9	126.0	68.7	98.7
SEM	49.9	38.5	24.8	44.2	36.5	28.7	52.7	37.4	57.4	57.1	51.4	57.4	57.1	51.4	28.1	40.3

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 17 (1 of 2)

VENTILATORY RESPONSES TO INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
30:30 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS								DIFFERENCES			
		-----						-----					
PRE EXP 1 ATA	START EXP 2 ATA	3.6	5.6	7.6	9.6	11.6	12.6	13.6	END EXP 2 ATA	POST EXP 1 ATA	END- START 2 ATA	POST- PRE 1 ATA	
Expiratory Minute Volume (L/min)													
N	6	6	6	6	6	6	4	4	6	6	6	6	
MEAN	7.30	10.20	10.10	10.02	9.58	10.22	10.40	9.98	10.32	8.28	-0.06	0.98	
SD	0.62	1.31	0.64	1.41	1.13	2.13	0.63	1.82	1.28	0.72	2.53	1.30	
SEM	0.25	0.53	0.26	0.58	0.46	0.87	0.31	0.91	0.52	0.29	1.03	0.53	
Respiratory Rate (Breaths/min)													
N	6	6	6	6	6	6	4	4	6	6	6	6	
MEAN	13.2	14.8	14.5	14.2	14.2	15.0	16.3	15.5	15.7	16.8	1.7	3.6	
SD	3.6	4.1	2.1	0.8	1.9	2.4	3.0	4.1	5.0	5.0	4.1	4.8	
SEM	1.5	1.7	0.8	0.3	0.8	1.0	1.8	2.1	2.1	2.1	1.7	2.0	
Tidal Volume (L)													
N=6	6	6	6	6	6	6	4	4	6	6	6	6	
MEAN	0.58	0.73	0.71	0.71	0.68	0.69	0.67	0.66	0.73	0.55	-0.03	-0.03	
SD	0.14	0.21	0.08	0.10	0.08	0.13	0.19	0.06	0.31	0.25	0.25	0.14	
SEM	0.06	0.09	0.03	0.04	0.03	0.05	0.10	0.03	0.13	0.10	0.10	0.06	

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 17 (2 of 2)

VENTILATORY RESPONSES TO INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
30:30 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS					Rate Of CO ₂ Elimination (L/min)					DIFFERENCES			
		-----					-----					-----			
PRE EXP 1 ATA	START EXP 2 ATA	3.6	5.6	7.6	9.6	11.6	12.6	13.6	END EXP 2 ATA	POST EXP 1 ATA	END- START 2 ATA	POST- PRE 1 ATA			
N	6	6	6	6	6	4	4	4	6	6	6	6			
MEAN	0.23	0.25	0.27	0.27	0.25	0.25	0.26	0.25	0.25	0.23	-0.01	0.00			
SD	0.03	0.02	0.01	0.03	0.04	0.05	0.05	0.02	0.02	0.03	0.05	0.03			
SEM	0.01	0.01	0.01	0.01	0.02	0.03	0.02	0.01	0.01	0.01	0.02	0.01			

		End-Tidal PCO ₂ (mm Hg)												
		-----					-----				-----			
N	6	6	6	6	6	6	4	4	6	6	6	6	6	
MEAN	40.2	32.8	34.9	36.2#	35.8	35.6	32.6	32.3	33.2	37.2	-0.6	-3.0		
SD	2.0	3.4	3.2	2.8	2.9	2.7	2.2	3.2	3.9	3.6	2.1	3.5		
SEM	0.8	1.4	1.3	1.2	1.2	1.1	1.1	1.6	1.6	1.5	0.9	1.4		

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 18 (1 of 2)
EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON PULMONARY FUNCTION IN MAN
30:30 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS -----								DIFFERENCES				
		PRE EXP 1 ATA	START EXP 2 ATA	4.0	6.0	8.0	10.0	12.0	13.0	14.0	END EXP 2 ATA	POST EXP 1 ATA	END- START 2 ATA	POST- PRE 1 ATA
Forced Vital Capacity (L)														
N		6	6	6	6	6	6	6	6	4	6	6	6	6
MEAN		5.27	5.17	5.14	5.07	4.83#	4.80#	4.82#	4.86#	4.73	4.83	4.86	-0.34*	-0.41*
SD		1.04	0.93	0.95	0.82	0.74	0.70	0.90	0.76	0.81	0.73	0.90	0.24	0.33
SEM		0.43	0.38	0.39	0.34	0.30	0.29	0.37	0.31	0.40	0.30	0.37	0.10	0.14
One Second Forced Expired Volume (L)														
N		6	6	6	6	6	6	6	6	4	6	6	6	6
MEAN		4.29	3.81	3.81	3.79	3.56#	3.68	3.71	3.67	3.56	3.70	4.09	-0.11	-0.20
SD		0.55	0.37	0.33	0.38	0.29	0.33	0.46	0.35	0.17	0.47	0.50	0.29	0.21
SEM		0.22	0.15	0.13	0.15	0.12	0.14	0.19	0.14	0.09	0.19	0.20	0.12	0.09

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).
Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 18 (2 of 2)
EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON PULMONARY FUNCTION IN MAN
30:30 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS -----								DIFFERENCES					
		PRE EXP 1 ATA	START EXP 2 ATA	4.0	6.0	8.0	10.0	12.0	13.0	14.0	END EXP 2 ATA	POST EXP 1 ATA	END- START 2 ATA	POST- PRE 1 ATA	
Peak Expiratory Flow Rate (L/sec)															
N		6	6	6	6	6	6	6	6	4	6	6	6	6	
MEAN		9.43	7.28	7.70	7.68	6.60	6.67	6.59	6.45	7.65	7.06	8.82	-0.21	-0.61	
SD		1.45	0.84	1.63	1.63	1.81	1.95	1.10	1.16	3.14	1.84	1.53	1.42	0.94	
SEM		0.59	0.34	0.67	0.66	0.74	0.80	0.45	0.47	1.57	0.75	0.63	0.58	0.38	

Maximal Mid-Expiratory Flow Rate (L/sec)

		6	6	6	6	6	6	6	6	4	6	6	6	6
N		6	6	6	6	6	6	6	6	6	6	6	6	6
MEAN		4.55	3.31	3.40	3.41	3.14	3.43	3.45	3.45	3.48	3.47	4.51	0.16	-0.04
SD		1.00	0.64	0.58	0.76	0.79	0.83	0.74	0.90	1.12	0.98	0.78	0.59	0.49
SEM		0.41	0.26	0.24	0.31	0.32	0.34	0.30	0.37	0.56	0.40	0.32	0.24	0.20

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).
Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 19

EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON PULMONARY FUNCTION IN MAN 30:30 OXYGEN:NORMOXIC SEQUENCE

	PRE EXP	POST EXP	POST- PRE Δ	PRE EXP	POST EXP	POST- PRE Δ
	Slow Vital Capacity (L)			Inspiratory Capacity (L)		
N	6	6	6	6	6	6
MEAN	5.35	5.02	-0.34*	3.43	2.91	-0.52*
SD	0.96	0.85	0.32	0.59	0.42	0.27
SEM	0.39	0.35	0.13	0.24	0.17	0.11
	Expiratory Reserve Volume (L)			Total Lung Capacity (L)		
N	6	6	6	6	6	6
MEAN	1.92	2.09	0.17	6.27	6.23	-0.04
SD	0.43	0.47	0.26	1.13	1.09	0.23
SEM	0.18	0.19	0.11	0.46	0.44	0.10
	CO Diffusing Capacity (ml/CO/mm Hg/min)			Density Dependence of Flow (% $\Delta \dot{V}_{max_{50}}$)		
N	6	6	6	6	6	6
MEAN	34.7	33.1	-1.7*	50.6	45.2	-5.5
SD	7.0	6.8	1.1	10.9	36.3	27.5
SEM	2.8	2.8	0.4	4.5	14.8	11.2
	Airway Resistance (cm H ₂ O/L/sec)			Specific Lung Compliance (L/cm H ₂ O/L)		
N	6	6	6	6	6	6
MEAN	2.65	2.45	-0.20	0.116	0.089	-0.027*
SD	0.74	0.60	0.33	0.032	0.030	0.011
SEM	0.30	0.30	0.13	0.013	0.012	0.004

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).

Appendix Table 20

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON ARTERIAL OXYGENATION AND ACID-BASE STATE IN MAN
30:30 OXYGEN:NORMOXIC SEQUENCE**

	PAO ₂ (mm Hg)	PaO ₂ (mm Hg)	PO ₂ (mm Hg)	PCO ₂ (mm Hg)	pH	[HCO ₃ ⁻] (meq/L)	PAO ₂ (mm Hg)	PaO ₂ (mm Hg)	PO ₂ (mm Hg)	PCO ₂ (mm Hg)	pH	[HCO ₃ ⁻] (meq/L)
At Rest Breathing Air At 1.0 ATA												
N	6	6	6	6	6	6	6	6	6	6	6	6
MEAN	108.1	97.3	10.8	39.4	7.405	24.4	105.7	96.4	9.2	39.4	7.398	24.1
SD	11.4	11.8	4.7	5.6	0.045	1.4	5.5	5.2	3.2	3.4	0.015	1.7
SEM	4.7	4.8	1.9	2.3	0.018	0.6	2.2	2.1	1.3	1.4	0.006	0.7
During Exercise Breathing Air At 1.0 ATA												
N	6	6	6	6	6	6	6	6	6	6	6	6
MEAN	108.3	92.9	15.4	40.7	7.375	23.6	108.3	90.7	17.6	39.2	7.376	22.7
SD	10.3	15.2	6.4	5.6	0.035	2.3	5.8	8.9	7.9	4.2	0.022	2.3
SEM	4.2	6.2	2.6	2.3	0.014	0.9	2.4	3.6	3.2	1.7	0.009	0.9
At Rest Breathing Oxygen at 2.0 ATA												
N	6	6	6	6	6	6	6	6	6	6	6	6
MEAN	1435	1368	67	36.1	7.438	24.3	1434	1338	96	35.4	7.433	23.5
SD	4	25	26	1.9	0.018	1.1	4	39	38	3.5	0.027	2.0
SEM	1	10	11	0.8	0.007	0.4	2	16	16	1.4	0.011	0.8

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).

Appendix Table 21

**EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA
ON RESPIRATORY AND SKELETAL MUSCLE STRENGTH
30:30 OXYGEN:NORMOXIC SEQUENCE**

PRE EXP	POST EXP	POST- PRE Δ	PRE EXP	POST EXP	POST- PRE Δ
------------	-------------	----------------	------------	-------------	----------------

Maximum Inspiratory Pressure (cm H₂O)

At Residual Volume

**At Functional Residual
Capacity**

N	6	6	6	6	6	6
MEAN	146.5	127.0	-19.5	119.4	115.4	-4.0
SD	12.2	22.2	30.0	21.9	22.4	23.2
SEM	5.0	9.1	12.3	9.0	9.2	9.5

Maximum Expiratory Pressure (cm H₂O)

At Total Lung Capacity

**At Functional Residual
Capacity**

N	6	6	6	6	6	6
MEAN	137.5	113.1	-24.5	131.6	116.3	-15.3
SD	39.3	26.2	36.1	29.4	35.6	21.3
SEM	16.0	10.7	14.7	12.0	14.5	8.7

**Maximum Handgrip
Strength (Kg)**

**Duration for 80% Maximum
Handgrip (Sec)**

N	6	6	6	6	6	6
MEAN	50.3	46.7	-3.6	42.7	35.3	-7.4
SD	8.2	7.4	4.0	24.2	11.4	21.6
SEM	3.3	3.0	1.6	9.9	4.6	8.8

* Difference from control significantly significant by paired t-test ($p \leq 0.05$).

Appendix Table 22 (1 of 2)

EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON CARDIOVASCULAR FUNCTION AND DEEP BODY TEMPERATURE IN MAN
30:30 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS					DIFFERENCES					
		-----					-----					
PRE	START	4.0	6.0	8.0	10.0	12.0	13.0	14.0	END	POST	END- START	POST- PRE
EXP	EXP								EXP	EXP		
1 ATA	2 ATA								2 ATA	1 ATA	2 ATA	1 ATA

Heart Rate (Beats/min)

N	6	6	6	6	6	6	6	4	6	6	6	6
MEAN	57.5	53.8	53.0	48.7	53.7	54.2	59.5	61.2	60.0	62.2	65.5	8.3*
SD	6.7	5.5	5.7	5.0	8.4	5.1	8.8	2.9	5.2	8.7	9.5	7.9
SEM	2.7	2.2	2.3	2.1	3.4	2.1	3.6	1.2	2.6	3.6	3.9	3.2
												8.7
												3.5

Stroke Volume (ml)

N	6	6	6	6	6	6	6	4	6	6	6	6
MEAN	88.5	102.6	89.9	100.5	91.8	93.9	81.2	85.0	80.3	82.2	72.4	20.4
STD	23.4	25.7	27.7	33.7	30.1	23.3	32.9	15.1	18.5	14.7	16.1	21.8
SEM	9.6	10.5	11.3	13.8	12.3	9.5	13.4	6.1	9.2	6.0	6.6	8.9
												10.9
												16.1
												26.8
												10.9

Cardiac Output (L/min)

N	6	6	6	6	6	6	6	4	6	6	6	6
MEAN	5.06	5.58	4.75	4.95	5.05	5.08	4.92	5.24	4.79	5.19	4.80	-0.39
SD	1.31	1.72	1.60	1.91	2.14	1.26	2.55	1.14	0.99	1.66	1.40	1.41
SEM	0.53	0.70	0.65	0.78	0.87	0.52	1.04	0.47	0.50*	0.68	0.57	0.58
												0.59
												-0.26
												1.44
												0.59

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).

Appendix Table 22 (2 of 2)

EFFECTS OF INTERMITTENT OXYGEN EXPOSURE AT 2.0 ATA ON CARDIOVASCULAR FUNCTION AND DEEP BODY TEMPERATURE IN MAN
30:30 OXYGEN:NORMOXIC SEQUENCE

		OXYGEN EXPOSURE HOURS							DIFFERENCES							
		START EXP 2 ATA		4.0	6.0	8.0	10.0	12.0	13.0	14.0	END EXP 2 ATA		POST EXP 1 ATA	END- START 2 ATA	POST- PRE 1 ATA	
Mean Arterial Blood Pressure (mm Hg)																
N	6	6	6	6	6	6	6	6	6	4	6	6	6	6	6	
MEAN	85.8	87.6	91.3	90.3	95.4	94.0	92.3	92.8	92.3	92.3	95.6	96.1	96.1	8.1	10.3	
SD	11.2	13.5	9.2	10.1	11.7	15.5	9.9	10.6	9.0	9.0	11.9	9.8	9.8	10.7	9.8	
SEM	4.6	5.5	3.8	4.1	4.8	6.3	4.0	4.3	4.5	4.5	4.9	4.0	4.0	4.4	4.0	
Systemic Vascular Resistance (dyne sec/cm)																
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
MEAN	17.78	17.07	20.99	20.91	21.52	19.66	22.66	18.54	13.11	13.11	19.68	21.64	21.64	2.61	3.86	
SD	4.37	5.96	6.66	8.51	7.81	6.10	10.01	5.32	10.42	10.42	5.82	7.13	7.13	4.80	6.14	
SEM	1.78	2.44	2.72	3.48	3.19	2.49	4.09	2.17	4.25	4.25	2.37	2.91	2.91	1.96	2.51	
Deep Body Temperature (°C)																
N	6	6	6	6	6	6	6	6	6	4	6	6	6	6	6	
MEAN	37.0	37.0	37.1	36.8	36.6#	36.7	37.1	37.1	37.1	37.1	37.3	37.3	37.3	0.2	0.3*	
STD	0.1	0.2	0.3	0.4	0.2	0.3	0.2	0.2	0.2	0.2	0.3	0.1	0.1	0.3	0.0	
SEM	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	

* Difference from control statistically significant by paired t-test ($p \leq 0.05$).# Difference from 2.0 ATA control statistically significant by ANOVA ($p \leq 0.05$).